IN THE U.S. PATENT AND TRADEMARK OFFICE

APPLICATION NUMBER	:	09/673,871
PATENT NUMBER	:	7,348,361
FILING DATE	:	November 30, 2000
ISSUE DATE	:	March 25, 2008
INVENTOR(S)	:	Marti *et al.*

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450
Mail Stop Patent Ext.

APPLICATION FOR EXTENSION OF THE TERM OF U.S. PATENT NO. 7,348,361 UNDER 35 U.S.C. § 156 FOR CYSVIEW™ (HEXAMINOLEVULINATE HYDROCHLORIDE) FOR INTRAVESICAL SOLUTION

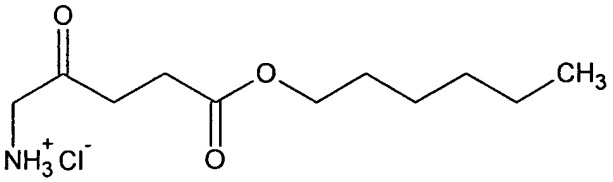
Sir:

Photocure ASA represents that it is the duly authorized agent of Norbert Lange, École Polytechnique Fédérale de Lausanne, and University of Lausanne, and that the same are collectively the co-owners of the entire right, title, and interest in and to U.S. Patent No. 7,348,361 ("the '361 patent," attached as **Exhibit A**), as detailed herein. The '361 patent, entitled SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES, issued on March 25, 2008 to Alexandre Marti, Norbert Lange, Matthieu Zellweger, Georges Wagnières, Hubert Van Den Bergh, Patrice Jichlinski, and Pavel Kucera. Photocure ASA is the marketing applicant for CYSVIEW™ (hexaminolevulinate hydrochloride) for Intravesical Solution (Cysview™ label attached as **Exhibit B**), which received marketing approval from the U.S. Food and Drug Administration ("FDA") on May 28, 2010.

Pursuant to 35 U.S.C. § 156(d) and 37 C.F.R. §§ 1.710 *et seq.*, the co-owners of the '361 patent hereby submit through their agent Photocure ASA this application for an extension of the term of the '361 patent. *See* Statements Under 37 C.F.R. § 3.73(b) and Appointments of Agent (attached as **Exhibits C-E**). An extension of 564 days is requested based on the regulatory review period of the Cysview™ product as set forth below. The undersigned is authorized to represent Photocure ASA in this application. *See* Power of Attorney (attached as **Exhibit F**).

Paragraphs (1) through (15) below correspond to paragraphs (1) through (15) of 37 C.F.R. § 1.740(a).

(1) The approved product is hexaminolevulinate hydrochloride, approved for marketing as CYSVIEW™ for Intravesical Solution. Hexaminolevulinate hydrochloride is an optical imaging drug that in solution form is instilled intravesically for use with photodynamic blue light cystoscopy as an adjunct to white light cystoscopy. The chemical formula for hexaminolevulinate hydrochloride is $C_{11}H_{21}NO_3 \cdot HCl$. Its molecular weight is 251.76 and it has the following structural formula:



CYSVIEW™ (hexaminolevulinate hydrochloride) for Intravesical Solution is intended for intravesical administration only after reconstitution with the supplied 50 mL DILUENT. CYSVIEW™ (hexaminolevulinate hydrochloride) for Intravesical Solution and DILUENT for Cysview™ are supplied together as a kit.

CYSVIEW™ (hexaminolevulinate hydrochloride) for Intravesical Solution is supplied as a sterile, non-pyrogenic, freeze-dried, white to off-white or pale yellow, powder containing 100 mg of hexaminolevulinate hydrochloride (equivalent of 85 mg of hexaminolevulinate) in a 10 mL clear glass vials. The DILUENT for Cysview™ is a sterile, non-pyrogenic solution (pH 6) containing 0.61 mg/ mL disodium hydrogen phosphate, 0.58 mg/mL of potassium dihydrogen phosphate, 7.02 mg/mL of sodium chloride, hydrochloric acid, sodium hydroxide, and water for injection. It is a clear, colorless solution, free from visible particles, and is provided in a 50 mL polypropylene vial.

The reconstituted solution of Cysview™ contains 2 mg/ml of hexaminolevulinate hydrochloride and is colorless to pale yellow. It is free from visible particles and has a pH between 5.7 and 6.2.

Cysview™ is indicated for use in the cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy. Cysview™ is used with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system to perform cystoscopy with the blue light setting (Mode 2) as an adjunct to the white light setting (Mode 1). *See* Cysview label §§ 1, 11.

(2) Regulatory review of CYSVIEW™ (hexaminolevulinate hydrochloride) for Intravesical Solution occurred under section 505(b) of the Federal Food, Drug and Cosmetic Act, codified at 21 U.S.C. § 355(b).

(3) CYSVIEW™ (hexaminolevulinate hydrochloride) for Intravesical Solution received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug and Cosmetic Act on May 28, 2010. It was approved for use in the cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy.

(4) The only active ingredient of CYSVIEW™ (hexaminolevulinate hydrochloride) for Intravesical Solution is hexaminolevulinate, as its hydrochloride salt. Hexaminolevulinate, any salt or ester thereof, hexaminolevulinate hydrochloride, and any salt or ester thereof, have not previously been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. § 1.720(f). The last day on which this application could be submitted is July 26, 2010.

(6) The patent for which an extension is being sought is as follows:

Inventors: Alexandre Marti, Norbert Lange, Matthieu Zellweger, Georges Wagnières, Hubert Van Den Bergh, Patrice Jichlinski, and Pavel Kucera

Patent No.: 7,348,361

Issue date: March 25, 2008

Expiration: April 22, 2019

(7) A copy of the '361 patent is attached hereto as Exhibit A.

(8) No terminal disclaimer, certificate of correction or reexamination certificate has been issued. No maintenance fee payments have yet been due.

(9) The '361 patent claims the approved Cysview™ product and a method of using the Cysview™ product. The applicable patent claims and the manner in which each claim reads on the approved product follow.

Claim 1:

Claim 1 reads as follows:

> 1. A pharmaceutical preparation to be administered to a patient for at least one of diagnosis and treatment of tissue or a cell lesion followed by localized irradiation using a beam emitted by a source of light energy, the pharmaceutical preparation comprising: a physiologically acceptable solvent; and ALA hexylester (h-ALA) for generating

protoporphyrin IX (PpIX) which is present in the pharmaceutical preparation at a concentration of less than 1% by weight.

Cysview™ for Intravesical Solution is intended for intravesical administration to patients only after reconstitution with the supplied 50 mL diluent. The reconstituted solution of Cysview™ contains 2 mg/ml of hexaminolevulinate hydrochloride (about 0.2% by weight) in a solution for administration to patients (which is equivalent to about 0.17% by weight of hexaminolevulinate). *See* Cysview™ package insert section 11. Claim 1 therefore reads on the approved Cysview™ product.

Claim 2:

Claim 2 reads as follows:

> 2. The pharmaceutical preparation according to claim 1, wherein the ALA hexylester (h-ALA) is dissolved in a solvent which is compatible with a human organism.

Since claim 1 claims a pharmaceutical preparation that encompasses the Cysview™ product, and because the Cysview™ solution is approved for administration to humans, claim 2 reads on the approved product.

Claim 3:

Claim 3 reads as follows:

> 3. The pharmaceutical preparation according to claim 2, wherein the solvent is selected from the group consisting of sterilized water, physiological NaCl solution, and a phosphate buffer solution.

Since claim 2 claims a pharmaceutical preparation that encompasses the Cysview™ product, and the package insert indicates that the diluent for Cysview™ is an aqueous solution that contains, in part, 0.61 mg/ mL disodium hydrogen phosphate and 0.58 mg/mL of potassium dihydrogen phosphate, and is thus a phosphate buffer solution, claim 3 reads on the approved product.

Claim 4:

Claim 4 reads as follows:

> 4. The pharmaceutical preparation according to claim 2, wherein the pharmaceutical preparation contains a component to adjust the pH of the pharmaceutical preparation to a physiological value ranging from about 4.8 to about 8.1.

Since claim 2 claims a pharmaceutical preparation that encompasses the Cysview™ product, and because the Cysview™ package insert indicates that the reconstituted solution of Cysview™ has a pH of 5.7 to 6.2, within the claim-recited range, and contains hydrochloric acid and sodium hydroxide, which, being an acid and a base, function to adjust the pH of the solution, claim 4 reads on the approved product.

Claim 8:

Claim 8 reads as follows:

> 8. The pharmaceutical preparation according to claim 1, wherein the ALA hexylester (h-ALA) is dissolved in a solvent which is compatible with an animal organism.

Since claim 1 claims a pharmaceutical preparation that encompasses the Cysview™ product, and the Cysview™ solvent is approved for administration to humans and therefore is compatible with an animal organism, claim 8 reads on a the approved product.

Claim 9:

Claim 9 reads as follows:

> 9. The pharmaceutical preparation according to claim 8, wherein the solvent is selected from the group consisting of sterilized water, physiological NaCl solution, and a phosphate buffer solution.

Since claim 8 claims a pharmaceutical preparation that encompasses the Cysview™ product, and because the package insert indicates that the diluent for Cysview™ is an aqueous solution that contains, in part, 0.61 mg/ mL disodium hydrogen phosphate and 0.58 mg/mL of potassium dihydrogen phosphate, and is thus a phosphate buffer solution, Claim 9 reads on the approved product.

Claim 10:

Claim 10 reads as follows:

> 10. The pharmaceutical preparation according to claim 8, wherein the pharmaceutical preparation contains a component to adjust the pH of the pharmaceutical preparation to a physiological value ranging from about 4.8 to about 8.1.

Since claim 8 claims a pharmaceutical preparation that encompasses the Cysview™ product, and because the Cysview™ package insert indicates that the reconstituted solution of Cysview™ has a pH of 5.7 to 6.2, within the claim-recited range, and contains hydrochloric acid and sodium hydroxide, which, being an acid and a base, function to adjust the pH of the solution, claim 10 reads on the approved product.

Claim 11:

Claim 11 reads as follows:

> 11. The pharmaceutical preparation according to claim 1, wherein, following administration of the pharmaceutical preparation to the patient and irradiation of the tissue or the cell lesion by the source of light energy, a fluorescence emitted by protoporphyrin IX (PpIX) generated by the ALA hexylester (h-ALA) contained in the

pharmaceutical preparation is detected to facilitate diagnosis of the tissue or the cell lesion.

Since claim 1 claims a pharmaceutical preparation that encompasses the Cysview™ product, claim 11 reads on the approved product. According to the Cysview™ label, after instillation of the Cysview™ solution, the bladder is exposed to blue light and the tissue is examined for red fluorescence, which indicates the presence of a bladder mucosa abnormality. *See* Cysview™ label § 2.5. Such fluorescence is emitted by protoporphyrin IX ("PpIX"), which is generated by hexaminolevulate, a precursor in the formation of PpIX. *See id.* § 12.1.

Claim 14:

Claim 14 reads as follows:

> 14. A method of diagnosis of a tissue or a cell lesion in an organism, said method comprising: (a) administering to the organism the pharmaceutical preparation of claim 1 (b) irradiating the tissue or the cell lesion with a source of light energy; and (c) detecting fluorescence emitted by protoporphyrin IX (PpIX) generated by the ALA hexylester (h-ALA).

Claim 1 claims a pharmaceutical preparation that encompasses the Cysview™ product. According to the Cysview™ label, after instillation of the Cysview™ solution, the bladder is exposed to blue light and the tissue is examined for red fluorescence, by which a bladder mucosa abnormality can be detected. *See* Cysview™ label § 2.5. Such fluorescence is emitted by protoporphyrin IX ("PpIX"), for which hexaminolevulate is a precursor. *See id.* § 12.1. Claim 14 therefore reads on a method of using the approved product for its approved use.

Claim 15:

Claim 15 reads as follows:

> 15. The method of claim 14, wherein the concentration of the ALA hexylester (h-ALA) in the pharmaceutical preparation ranges from 0.01% by weight to 0.5% by weight.

Since claim 14 claims a method of using the approved product for its approved use, and because the solution of Cysview™ contains about 0.2% by weight of hexaminolevulinate hydrochloride (equivalent to about 0.17% by weight of hexaminolevulinate), claim 15 reads on a method of using the approved product for its approved use.

Claim 16:

Claim 16 reads as follows:

> 16. The method of claim 14, wherein the solvent is selected from the group consisting of sterilized water, physiological NaCl solution, and a phosphate buffer solution.

Since claim 14 claims a method of using the approved product for its approved use, and because the package insert indicates that the diluent for Cysview™ is an aqueous solution that contains, in part, 0.61 mg/ mL disodium hydrogen phosphate and 0.58 mg/mL of potassium dihydrogen phosphate, and is thus a phosphate buffer solution, Claim 16 reads on a method of using the approved product for its approved use.

Claim 17:

Claim 17 reads as follows:

> 17. The method of claim 14, wherein the pharmaceutical preparation contains a component to adjust the pH of the pharmaceutical preparation to a physiological value ranging from about 4.8 to about 8.1.

Since claim 14 claims a method of using the approved product for its approved use, and because the Cysview™ package insert indicates that the reconstituted solution of Cysview™ has a pH of 5.7 to 6.2, within the claim-recited range, and contains hydrochloric acid and sodium hydroxide, which, being an acid and a base, function to adjust the pH of the solution, claim 17 reads on a method of using the approved product for its approved use.

Claim 21:

Claim 21 reads as follows:

> 21. The method of claim 14, wherein the organism is a human or an animal.

Since claim 14 claims a method of using the approved product for its approved use, and because the Cysview™ solution is approved for and intended for administration to humans, Claim 21 reads on a method of using the approved product for its approved use.

(10) The relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are:

IND number:	51.224
IND effective date:	October 29, 2001
NDA number:	NDA 22-555
NDA submission date:	June 30, 2009
NDA approval date:	May 28, 2010

(11) As a brief description of the significant activities undertaken by the marketing applicant Photocure during the applicable regulatory review period with respect to the approved Cysview™ product and the significant dates applicable to such activities, attached hereto are **Exhibits G-I**. Exhibits G and H are a brief chronology of the IND No. 51.224 and NDA No. 22-555 communications with the FDA during the regulatory review period culminating with the approval of the Cysview™ product on May 28, 2010. (The tradename "Hexvix®," which recurs throughout Exhibits G-I, was the original name of the Cysview™ product.)

Exhibit I, included for the sake of completeness, is a brief chronology of the NDA No. 21-893 communications with the FDA during the regulatory review period. NDA No. 21-893 was filed earlier than No. 22-555 and, like No. 22-555, concerned the Cysview™ product (referred to therein as "Hexvix"). NDA No. 22-555 relies in part on information provided to the FDA in NDA No. 21-893, such as toxicology data relating to the Cysview™ product. Reviewer's guide in module 1.6.3 of NDA No. 22-555 describes NDA No. 21-893 and its relevance to No. 22-555.

(12) In the opinion of the applicant, the '361 patent is eligible for patent term extension under 35 U.S.C. § 156. An extension of 564 days is claimed. The eligibility for and length of the claimed extension were determined as follows:

(a) 35 U.S.C. 156(a)

The '361 patent claims a pharmaceutical product containing Cysview™, and methods of diagnosis using the Cysview™ product.

(b) 35 U.S.C. 156(a)(1)

The term of the '361 patent is due to expire April 22, 2019 and therefore has not expired before submission of this application.

(c) 35 U.S.C. 156(a)(2)

The term of the '361 patent has never been extended under 35 U.S.C. § 156(e)(1).

(d) 35 U.S.C. 156(a)(3)

The application for extension is submitted by the co-owners of the '361 patent, Norbert Lange, École Polytechnique Fédérale de Lausanne, and University of Lausanne, through their appointed agent Photocure ASA in accordance with the requirements of 35 U.S.C. §§ 156(d)(1)-(4) and the rules of the U.S. Patent and Trademark Office.

(e) 35 U.S.C. 156(a)(4)

The product (the active ingredient, including any salt or ester of the active ingredient) in Cysview™ has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. 156(a)(5)(A)

The permission for the commercial marketing or use of Cysview™ after the regulatory review period referred to in subsection (e) above is the first permitted commercial marketing or use of the product under section 505(b) of the Federal Food Drug and Cosmetic Act.

(g) 35 U.S.C. 156(c)(4)

No patent has been extended under 35 U.S.C. § 156(e)(1) for the regulatory review period that forms the basis for this application for extension of the term of U.S. Patent No. 7,348,361.

The length of extension of the patent term of the '361 patent claimed by applicant is 564 days, until November 06, 2020. The length of the extension was determined pursuant to 37 C.F.R. 1.775 as follows:

(a) 2802 The number of days in the period beginning on the date an exemption under subsection (i) of section 505 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product (October 29, 2001) and ending on the date the application was initially submitted for such product under that subsection (June 30, 2009) (*see* 37 C.F.R. 1.775(c)(1)).

(b) 333 The number of days in the period beginning on the date the application was initially submitted for the approved product under subsection (b) of section 505 of the Federal Food, Drug, and Cosmetic Act (June 30, 2009) and ending on the date such application was approved under such section (May 28, 2010) (*see* 37 C.F.R. 1.775(c)(2)).

(c) 3135 The sum of (a) and (b). This is the regulatory review period. (37 C.F.R. 1.775(c)).

(d) 2340 The number of days in the regulatory review period of (a) which were on and before the '361 patent issued. (37 C.F.R. 1.775(d)(1)(i)).

(e) 462 Subtract (d) from (a) for the days remaining in the regulatory review period of (a). (37 C.F.R. 1.775(d)(1)(i)).

(f) 0 The number of days in the regulatory review period during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence.[2] (37 C.F.R. 1.775(d)(1)(ii)).

(g) 333 Subtract (f) from (b). (37 C.F.R. 1.775(d)((1)(ii)).

(h) 462 Subtract (f) from (e). (37 C.F.R. 1.775(d)((1)(ii)).

(i) 231 Subtract from (h) one half of the days calculated in (h); half days will be ignored for the purposes of subtraction. (37 C.F.R. 1.775(d)(1)(iii)).

(j) 564 The sum of (g) and (i). (37 C.F.R. 1.775(d)(1)(iii)).

(k) 04/22/2019 The original term of the '361 patent, shortened by any terminal disclaimer.

(l) 11/06/2020 The original term of the patent as shortened by any terminal disclaimer plus the number of days in (j). (37 C.F.R. 1.775(d)(2)).

(m) 05/28/2024 The date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of

[2] There has been no such determination. To the best of applicant's knowledge, Photocure was diligent during the regulatory review period.

the Federal Food, Drug and Cosmetic Act plus 14 years. (37 C.F.R. 1.775(d)(3)).

(n) 11/06/2020 The earlier of (l) and (m). (37 C.F.R. 1.775(d)(4)).

(o) 04/22/2024 (k) plus 5 years. (37 C.F.R. 1.775(d)(5)(i)).

(p) 11/06/2020 The earlier of (n) and (o). (37 C.F.R. 1.775(d)(5)(ii)).

(13) The applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(14) Please charge the required fee ($1,120.00) pursuant to 37 C.F.R. 1.20(j) for receiving and acting upon this Application for Patent Term Extension of the '361 patent to deposit account 11-0600.

(15) Please address inquiries and correspondence to the undersigned.

An original and **four copies** of these application papers are hereby submitted.

Respectfully submitted,

Dated: July 23, 2010

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Exhibit A

US007348361B2

(12) **United States Patent**
Marti et al.

(10) **Patent No.: US 7,348,361 B2**
(45) **Date of Patent: Mar. 25, 2008**

(54) **SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES**

(75) Inventors: **Alexandre Marti**, Geneva (CH); **Norbert Lange**, Lausanne (CH); **Matthieu Zellweger**, Lausanne (CH); **Georges Wagnieres**, Morges (CH); **Hubert Van Den Bergh**, Goumoens-la-Ville (CH); **Patrice Jichlinski**, Le Mont-sur-Lausanne (CH); **Pavel Kucera**, Lausanne (CH)

(73) Assignee: **Ecole Polytechnique Federale de Lausanne**, Lausanne (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/673,871**

(22) PCT Filed: **Apr. 22, 1999**

(86) PCT No.: **PCT/CH99/00163**

§ 371 (c)(1),
(2), (4) Date: **Nov. 30, 2000**

(87) PCT Pub. No.: **WO99/53962**

PCT Pub. Date: **Oct. 28, 1999**

(65) **Prior Publication Data**

US 2003/0158258 A1 Aug. 21, 2003

(30) **Foreign Application Priority Data**

Apr. 22, 1998 (FR) 98 05425

(51) **Int. Cl.**
A61K 31/195 (2006.01)
A61K 49/00 (2006.01)
A61K 31/40 (2006.01)
A01N 43/38 (2006.01)

(52) **U.S. Cl.** **514/561**; 514/410; 424/9.61

(58) **Field of Classification Search** 514/410, 514/561, 814, 146; 424/9.61
See application file for complete search history.

(56) **References Cited**

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Primary Examiner—Sreeni Padmanabhan
Assistant Examiner—Yong S. Chong
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon LLP

(57) **ABSTRACT**

The invention concerns a 5-aminolevulinic acid ester (E-ALA) solution for producing a pharmaceutical preparation useful for diagnosing and/or treating tissue and/or cell pathologies by local radiation exposure using radiation emitted by a light source energy followed, in the case diagnosis, by detection of fluorescent protoporphyrin IX (PpIX). The E-ALA concentration in the solution is less than 1% and ranges between 0.01% and 0.5%. The low E-ALA concentration in the solution increases PpIX synthesis and homogenises its distribution in the cell layers while highly reducing the secondary toxicity for the treated cells.

31 Claims, No Drawings

SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES

TECHNICAL REALM

The present invention concerns a 5-aminolevulinic acid ester (E-ALA) for producing a pharmaceutical preparation used in the diagnosis and treatment of tissue and/or cellular pathologies by local radiation exposure using radiation emitted by a light source followed, in the case of diagnosis, by detection of fluorescence emitted by the substances for which the 5-aminolevulinic acid ester (ALA) or the E-ALA are precursors, particularly protoporphyrin IX (PpIX).

PRIOR ART

The use of compounds for which ALA or ALA esters (E-ALA) and particularly hexylester hydrochloric ALA (h-ALA) are precursors is well known in the diagnosis and/or treatment of lesions, particularly cancerous lesions. This principle is thoroughly discussed in patent Publication No. WO 96/28412. The solution may be administered orally or parenterally, for example, by intra-dermal, subcutaneous, intra-peritoneal or intravenous injection. It may also be administered topically, for example locally, by exposing the surface of the organ to be treated to an E-ALA or ALA solution. A pad saturated with such a solution can also be used during topical administration. The concentration of the ALA (E-ALA) ester solution mentioned in this publication ranges from 1 to 50% and preferably between 15% and 30%. However, this concentration generates essentially no PpIX in certain organs which are principally involved in this type of treatment, namely the bladder.

In the publications in the *Journal of Photochemistry and Photobiology B and Biology*, respectively, by Fin-Puches et al entitled "Primary Clinical Response and Long-Term Follow-Up of Solar Keratoses Treated with Topically Applied 5-Aminolevulinic Acid and Irradiation by Different Wave Bands of Light," and by Chang et al entitled "The Efficacy of an Iron Chelator (CP94) in Increasing Cellular Protoporphyrin IX Following Intravestical 5-Aminolaevulinic Acid Administration: An In Vivo Study," as well as the article in *Nouvelles Dermatologiques [Dermatology News]* by P. Thomas entitled "Photothérapie Dynamique Topique" ["Dynamic Topical Phototherapy"], the product used in treatment is ALA and not an ALA ester, which vary greatly in concentration. The ALA concentrations used are actually a minimum of 45 to 60 times higher than what is required when using an ALA ester solution (E-ALA).

Administering this substance in such strong concentrations has proven toxic to human tissue in certain instances. This toxicity, present even in the absence of light source radiation, can seriously deter generation of protoporphyrin IX (PpIX). For this reason, such concentrations either cannot be used in certain cases or are not ideal for the detection and treatment of lesions.

Furthermore, the time required to activate the active principles induced by the medicated solution is extremely long if free 5-aminolevulinic acid, that is, non-esterized ALA, is used. For this reason diagnosis and treatment using free ALA can only take place in a hospital setting, since the patient must frequently be immobilized for a very long period of time, approximately 5 hours.

In a climate where the cost of medical care is generally being reduced and preference is given to home health care, office treatment or one-day hospital care, the current treatment procedures are not only burdensome and restrictive for the patient, but costly to health insurance companies and the community.

Despite the technological progress which the use of ALA or E-ALA has contributed in terms of early diagnosis and effective treatment of certain afflictions, there are some major obstacles to its widespread use.

DESCRIPTION OF THE INVENTION

The goal of the present invention is to overcome these obstacles through the use of a solution designed for the diagnosis and/or treatment of cancerous lesions, particularly in the field of urology, administered in concentrations that will not prejudice biosynthesis of the active compounds and which is demonstrably very effective when applied for relatively short periods of time, making it appropriate for use in one-day clinics or even doctors' offices. Specifically, this solution must foster strong PpIX accumulation over a minimum time period and very thorough PpIX distribution throughout the treated tissue.

This goal is achieved using a 5-aminolevulinic acid ester (E-ALA) such as that defined in the preamble, characterized in that the concentration C of E-ALA in the solution is less than 1% and ranges from 0.01% to 0.5% ($0.01\% \leqq C \leqq 0.5\%$).

It has been shown in practice that use of a very low concentration of E-ALA in the solution increases PpIX synthesis and homogenizes distribution throughout the cellular layers, while at the same time greatly reducing secondary toxicity of the solution to the treated cells. This becomes even more important because when treating a tumor with dynamic phototherapy, the rapid photobleaching reduces PpIX concentration; complete destruction of the tumor implies an elevated initial accumulation of intracellular PpIX and thorough distribution throughout the layers of the tumor.

Advantageously, the ALA (E-ALA) ester producing the best results is hexylester hydrochloride ALA (h-ALA).

The solution is preferably produced by dissolving the ALA (E-ALA) ester in a solvent compatible with human or animal organisms.

Said solvent is advantageously selected from the following substances: sterilized filtered water, physiological NaCl solution, phosphate buffer solutions, with phosphate, or alcohol.

In its preferred form, the solution comprises a component for adjusting the PH to a physiological value ranging from 4.8 to 8.1.

In an advantageous form, the solution may comprise a complementary substance to prevent the transformation of the PpIX into a heme by iron complexing in the living cells.

Said complementary substance may be an EDTA (ethylene diamine tetmacetate) or deferoxamine mesylate (DESFERAL).

PREFERRED EMBODIMENT OF THE INVENTION

The present invention will be better understood with reference to the following description of a preferred embodiment of the solution according to the invention and its variations, and by way of illustration, a particularly advantageous application of the solution in the diagnosis and/or treatment of lesions inside a cavity in a human or animal organism, such as the bladder.

A 5-aminolevulinic acid solution (E-ALA) is prepared by dissolving said substance, which may be an amorphous powder or in crystalline form, in an appropriate solvent compatible with in vivo use. By way of example, this solution may consist of sterilized demineralized water, physiological NaCl solution containing approximately 9% NaCl, a phosphate buffer solution, an alcohol, or a solution containing alcohol or the like.

The solution can be completed by the addition of a complementary substance to prevent the PpIX from transforming into a heme by iron complexing in the living cells. This complementary substance may be an EDTA (ethylene diamine tetraacetate) or deferoxamine mesylate (DESFERAL).

The solution can be completed by the addition of a complementary substance to prevent the PpIX from transforming into a heme by iron complexing in the living cells. This complementary substance may be an EDTA (tetra acetate diaminoethyl), deferoxamine or desferal.

One especially interesting application is the diagnosis and treatment of cancerous lesions in the field of urology, particularly on the interior bladder walls.

According to one application, the solution may be administered topically, contacting the interior walls of the organ. The bladder is filled with about 50 ml of low concentration ALA (E-ALA) ester or ALA (h-ALA) hexylester solution, e.g., a concentration C (by weight) ranging from 0.01% and 0.5% and preferably equal to 0.2%.

Instillation may last from ½ hour to 7 hours, but preferably ranges from ½ hour to 4 hours.

Surprisingly, it has been noted that with the use of these low concentrations which differ considerably from the 15 to 30% concentrations currently used in this field, the ALA (E-ALA) ester is more effective, as measured by an increased presence of fluorescent protoporphyrin IX (PpIX) apparent at the location of the lesions on the interior bladder walls and improved protoporphyrin distribution in the cell layers. Furthermore, due to these low concentrations, cytotoxicity is reduced, which considerably decreases the risk of undesirable secondary effects. In particular, this reduced cytotoxicity favors the generation of the light sensitive and/or fluorescent substances to which free E-ALA or ALA are the precursors. Moreover, generating maximum PpIX shortens the time elapsing between administering the solution and performing the actual intervention.

One variation in application is defined as "fractionated topical method." It may comprise the following steps:

a first bladder instillation lasting from ½ hour to 3 hours, and preferably lasting for about 2 hours;

rinsing the bladder;

a second instillation lasting from ½ hour to 3 hours, and preferably lasting for about 2 hours;

rinsing the bladder.

After a waiting period of from 0 to 4 hours, and preferably for about 2 hours, fluorescent treatment and detection of the bladder can take place.

Topical solution of the ALA (E-ALA) ester solution or the ALA (h-ALA) hexylester solution may also be replaced by systemic application. In this case, the solution is administered either orally or parenterally either alone or in combination with compounds known as transporters, such as, for example, dimethylsulfoxide, glycine or the like, to enhance absorption and/or migration of the active substance, with the occurrence of the ALA (E-ALA) ester or the ALA (h-ALA) hexylester through the tissues and/or cells.

Finally, a way to activate penetration of the ALA (E-ALA) ester or the ALA (h-ALA) hexylester into the tissue or cells may consist of forming an iontophoresis on the walls of the organ concerned.

These phases are followed by one or more phototherapy and/or fluorescent treatment phases.

During phototherapy treatment, the walls of the organ concerned (for example, the bladder) are irradiated with a light beam called the excitant light, which may or may not be monochromatic, either continuously or sequentially, preferably situated in the spectrum domain ranging from 300 to 900 nanometers and preferably between 350 and 650 nanometers.

During phototherapy proceedings the lighting E applied to the bladder walls, which is light power per surface unit, ranges from 0.1 mW/cm^2 to 1 W/cm^2, and preferably between 5 mW/cm^2 and 500 mW/cm^2. This light induces a phototoxic reaction due to the presence of protoporphyrin IX (PpIX) in particular and/or its photo-products in the tissue. The light doses may be applied homogeneously over the entire wall of the organ, or selectively at only the locations that have been identified as having lesions. During fluorescent diagnosis, the bladder walls are irradiated using a beam with a spectral width ranging from 300 to 700 nanometers, and preferably from 350 to 650 nanometers. For these fluorescent diagnoses, the lighting E applied to the bladder walls (light power per surface unit) ranges from 1 mW/cm^2 and 1 mW/cm^2 and preferably between 50 mW/cm^2 to 500 mW/cm^2. The excitant light induces fluorescence in the substances to which E-ALA and especially h-ALA are precursors, particularly PpIX. This fluorescence is collected by an optical system and detected visually or by a specific, linear or matric detector such as a camera.

In addition to the advantages outlined above, the use of solutions with low ALA ester concentrations provides an inexpensive product for use in either phototherapy treatment or photodetection, at low production cost and with simplified Galenic pharmaceuticals.

The invention claimed is:

1. A pharmaceutical preparation to be administered to a patient for at least one of diagnosis and treatment of tissue or a cell lesion followed by localized irradiation using a beam emitted by a source of light energy, the pharmaceutical preparation comprising:

a physiologically acceptable solvent; and

ALA hexylester (h-ALA) for generating protoporphyrin IX (PpIX) which is present in the pharmaceutical preparation at a concentration of less than 1% by weight.

2. The pharmaceutical preparation according to claim 1, wherein the ALA hexylester (h-ALA) is dissolved in a solvent which is compatible with a human organism.

3. The pharmaceutical preparation according to claim 2, wherein the solvent is selected from the group consisting of sterilized water, physiological NaCl solution, and a phosphate buffer solution.

4. The pharmaceutical preparation according to claim 2, wherein the pharmaceutical preparation contains a component to adjust the pH of the pharmaceutical preparation to a physiological value ranging from about 4.8 to about 8.1.

5. The pharmaceutical preparation according to claim 1, wherein the pharmaceutical preparation comprises a complementary substance for preventing transformation of the protoporphyrin IX (PpIX) into a heme by iron complexing in the cells.

6. The pharmaceutical preparation according to claim 5, wherein the complementary substance is ethylene diamine tetraacetate (EDTA).

7. The pharmaceutical preparation according to claim 5, wherein the complementary substance is deferoxamine mesylate.

8. The pharmaceutical preparation according to claim 1, wherein the ALA hexylester (h-ALA) is dissolved in a solvent which is compatible with an animal organism.

9. The pharmaceutical preparation according to claim 8, wherein the solvent is selected from the group consisting of sterilized water, physiological NaCl solution, and a phosphate buffer solution.

10. The pharmaceutical preparation according to claim 8, wherein the pharmaceutical preparation contains a component to adjust the pH of the pharmaceutical preparation to a physiological value ranging from about 4.8 to about 8.1.

11. The pharmaceutical preparation according to claim 1, wherein, following administration of the pharmaceutical preparation to the patient and irradiation of the tissue or the cell lesion by the source of light energy, a fluorescence emitted by protoporphyrin IX (PpIX) generated by the ALA hexylester (h-ALA) contained in the pharmaceutical preparation is detected to facilitate diagnosis of the tissue or the cell lesion.

12. A pharmaceutical preparation to be administered to a patient for at least one of diagnosis and treatment of tissue or a cell lesion followed by localized irradiation using a beam emitted by a source of light energy, the pharmaceutical preparation comprising:

a physiologically acceptable solvent;

ALA hexylester (h-ALA) for generating protoporphyrin IX (PpIX) which is dissolved in the solvent at a concentration of less than 1% by weight;

a pH in the range of from about 4.8 to about 8.1; and

a complementary substance for preventing transformation of protoporphyrin IX (PpIX) into a heme by iron complexing in live cells, the complementary substance selected from ethylene diamine tetraacetate (BDTA), and deferoxamine mesylate.

13. The pharmaceutical preparation according to claim 12, wherein, following administering the pharmaceutical preparation to the patient and irradiation of the tissue or the cell lesion by the source of light energy, a fluorescence emitted by protoporphyrin IX (PpIX) generated by the ALA hexylester (h-ALA) contained in the pharmaceutical preparation is detected to facilitate diagnosis of the tissue or the cell lesion.

14. A method of diagnosis of a tissue or a cell lesion in an organism, said method comprising:

(a) administering to the organism the pharmaceutical preparation of claim 1

(b) irradiating the tissue or the cell lesion with a source of light energy; and

(c) detecting fluorescence emitted by protoporphyrin IX (PpIX) generated by the ALA hexylester (h-ALA).

15. The method of claim 14, wherein the concentration of the ALA hexylester (h-ALA) in the pharmaceutical preparation ranges from 0.01% by weight to 0.5% by weight.

16. The method of claim 14, wherein the solvent is selected from the group consisting of sterilized water, physiological NaCl solution, and a phosphate buffer solution.

17. The method of claim 14, wherein the pharmaceutical preparation contains a component to adjust the pH of the pharmaceutical preparation to a physiological value ranging from about 4.8 to about 8.1.

18. The method of claim 14, wherein the pharmaceutical preparation comprises a complementary substance for preventing transformation of the protoporphyrin IX (PpIX) into a heme by iron complexing in the cells.

19. The method of claim 18, wherein the complementary substance is ethylene diamine tetraacetate (EDTA).

20. The method of claim 18, wherein the complementary substance is deferoxamine mesylate.

21. The method of claim 14, wherein the organism is a human or an animal.

22. A method of treatment of a tissue or a cell lesion in an organism, said method comprising:

(a) administering to the organism a the pharmaceutical preparation of claim 1; and

(b) irradiating the tissue or the cell lesion with a source of light energy.

23. The method of claim 22, wherein the concentration of the ALA hexylester (h-ALA) in the pharmaceutical preparation ranges from 0.01% by weight to 0.5% by weight.

24. The method of claim 22, wherein the solvent is selected from the group consisting of sterilized water, physiological NaCl solution, and a phosphate buffer solution.

25. The method of claim 22, wherein the pharmaceutical preparation contains a component to adjust the pH of the solution to a physiological value ranging from about 4.8 to about 8.1.

26. The method of claim 22, wherein the pharmaceutical preparation comprises a complementary substance for preventing transformation of the protoporphyrin IX (PpIX) into a heme by iron complexing in the cells.

27. The method of claim 26, wherein the complementary substance is ethylene diamine tetraacetate (EDTA).

28. The method of claim 26, wherein the complementary substance is deferoxamine mesylate.

29. The method of claim 22, wherein the organism is a human or an animal.

30. The pharmaceutical preparation of claim 19, wherein the concentration of the ALA hexylester (h-ALA) ranges from 0.01% by weight to 0.5% by weight.

31. The pharmaceutical preparation of claim 12, wherein the concentration of the ALA hexylester (h-ALA) ranges from 0.01% by weight to 0.5% by weight.

* * * * *

Exhibit B

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Cysview safely and effectively. See full prescribing information for Cysview.

Cysview (hexaminolevulinate hydrochloride), for Intravesical Solution
For bladder instillation only
Initial U.S. Approval: 2010

----------INDICATIONS AND USAGE----------

Cysview is an optical imaging agent indicated for use in the cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy. Cysview is used with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system to perform cystoscopy with the blue light setting (Mode 2) as an adjunct to the white light setting (Mode 1).

Important Limitations of Use:

- Not a replacement for random bladder biopsies or other procedures used in the detection of bladder cancer. (1.1, 5.2)
- Not for repetitive use. (1.1, 5.1)

----------DOSAGE AND ADMINISTRATION----------

Training in blue light cystoscopy with the Karl Storz D-Light C PDD system is essential prior to the use of Cysview. (2.5)

- Reconstitute Cysview powder with all 50 mL of supplied DILUENT under aseptic conditions. (2.2)
- Use solution of Cysview shortly after reconstitution. If unable to use, the solution may be stored for up to 2 hours in a refrigerator at 2°-8°C (36°-46°F) in labeled syringe. Discard after 2 hours. (2.2, 16)
- Instill 50 mL of reconstituted solution of Cysview into the emptied bladder via an intravesical catheter. Retain in the bladder for 1 hour before evacuating and performing cystoscopic examination. (2.3, 2.5)
- First perform a complete cystoscopic examination of the entire bladder under white light and then repeat the examination of the entire bladder under blue light. Record and document information about location and appearance of suspicious lesions and areas seen under both white and blue light. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

Cysview (hexaminolevulinate hydrochloride) is supplied as a kit containing:

- A 10 mL glass vial containing 100 mg powder of Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution.
- A polypropylene vial containing 50 mL DILUENT for Cysview.
- One Luer Lock catheter adapter. (16)

Once reconstituted, the solution contains 2 mg/mL (8mmol/L) of hexaminolevulinate hydrochloride

----------CONTRAINDICATIONS----------

Do not use Cysview in patients with:

- porphyria,
- gross hematuria,
- BCG immunotherapy or intravesical chemotherapy within the past 90 days, or
- known hypersensitivity to hexaminolevulinate or aminolevulinate derivatives. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Anaphylaxis: have trained personnel and therapies available. (5.1).
- Failed Detection: Cysview may not detect all malignant lesions. Always perform white light cystoscopy (Mode 1) followed by blue light cystoscopy (Mode 2). Do not biopsy with blue light only. (5.2)
- False fluorescence may occur due to inflammation, cystoscopic trauma, scar tissue or previous bladder biopsy. (5.3)

----------ADVERSE REACTIONS----------

The most common adverse reaction reported in patients who received Cysview was bladder spasm, occurring in < 3% of patients, followed by dysuria, hematuria, bladder pain, procedural pain, urinary retention and headache, all occurring in ≤ 2% of patients. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy Category C: No human or animal data. Use only if clearly needed. (8.1)
- Nursing mothers: No human or animal data. Exercise caution when Cysview is administered to nursing mothers. (8.3)
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: X/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Cysview is indicated for use in the cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy. Cysview is used with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system to perform cystoscopy with the blue light setting (Mode 2) as an adjunct to the white light setting (Mode 1).

1.1 Limitations of Use

Cysview is not:

- a replacement for random bladder biopsies or other procedures used in the detection of bladder cancer *[see Warnings and Precautions (5.2)]*.
- for repetitive use. The potential risks associated with repetitive exposure, including sensitization and adverse effects of blue light have not been evaluated *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose for adults is 50 mL of reconstituted solution of Cysview (2.2), instilled into the bladder via a urinary catheter (2.3).

2.2 Reconstitution of Cysview

Cysview is supplied as a kit containing two vials: a clear glass vial labeled as Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution, containing 100 mg hexaminolevulinate hydrochloride as a powder, and a vial labeled as DILUENT for Cysview, containing 50 mL of the diluent in a polypropylene vial.

Perform all steps under aseptic conditions. Use gloves during the reconstitution procedure; skin exposure to hexaminolevulinate hydrochloride may increase the risk for sensitization to the drug.

Use a 50 mL syringe with a Luer Lock tip throughout the reconstitution procedure to ensure that the correct concentration (2mg/mL) of the drug is obtained and that a stable syringe-catheter connection is made for the bladder instillation of Cysview.

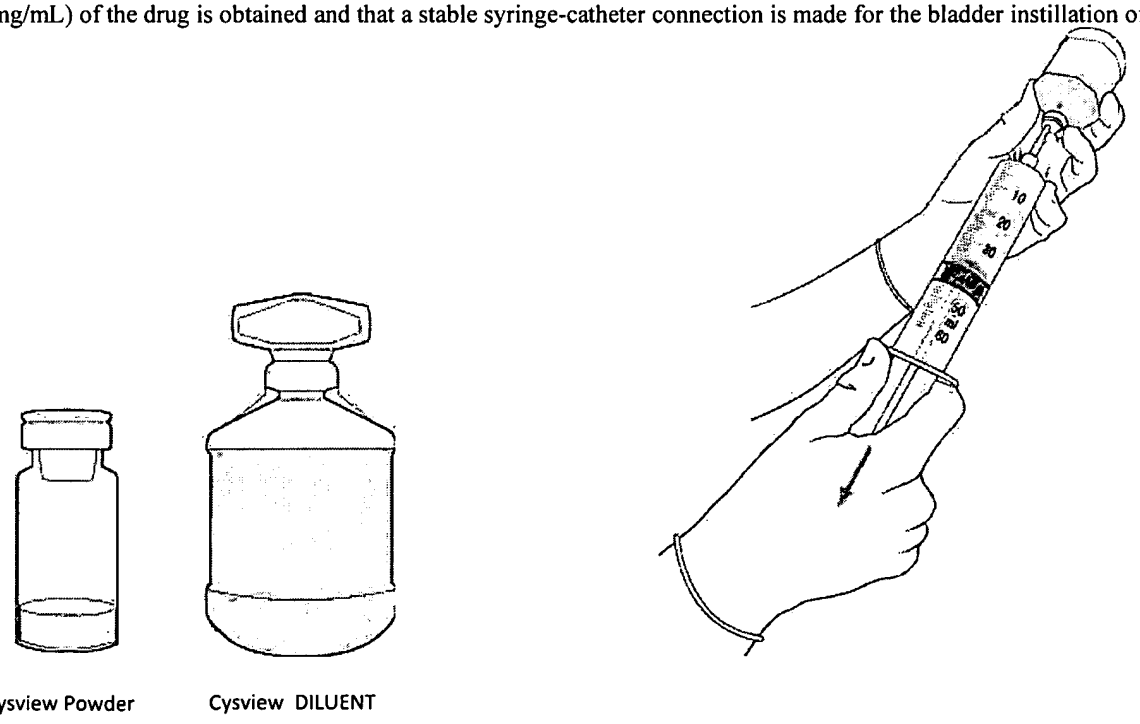


Figure 1.

1. Remove the cap from the sterile 50 mL syringe and carefully retain it for subsequent reattachment to the syringe (step 4). Attach a needle to the syringe and withdraw 50 mL of the diluent (Figure 1).

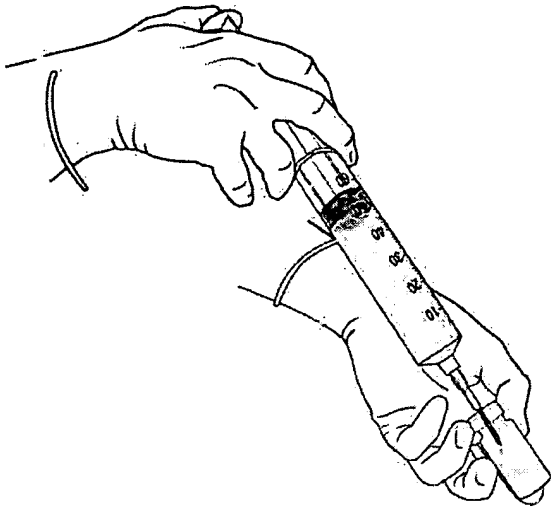


Figure 2.

2. Penetrate the stopper of the Cysview powder vial with the needle and inject 10 mL of the diluent from the syringe into the powder vial (Figure 2).

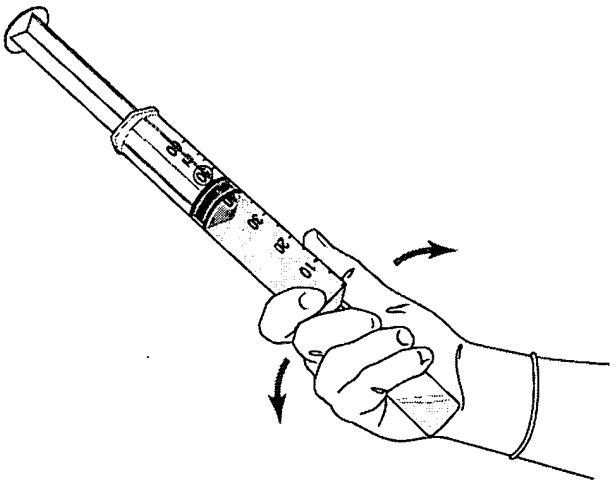


Figure 3.

3. Without withdrawing the needle from the vial, hold the powder vial and syringe in a firm grip (Figure 3) and gently shake to dissolve of the powder in the diluent. The powder normally dissolves almost immediately.

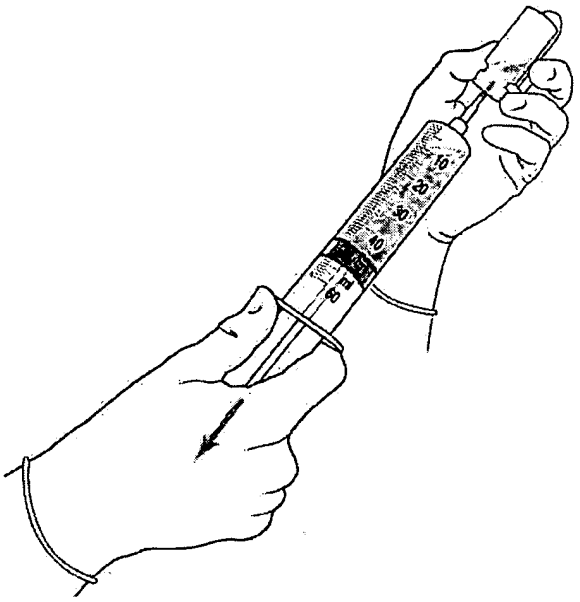


Figure 4.

4. Withdraw all of the dissolved solution from the powder vial (10 mL) into the 50 mL syringe (Figure 4).

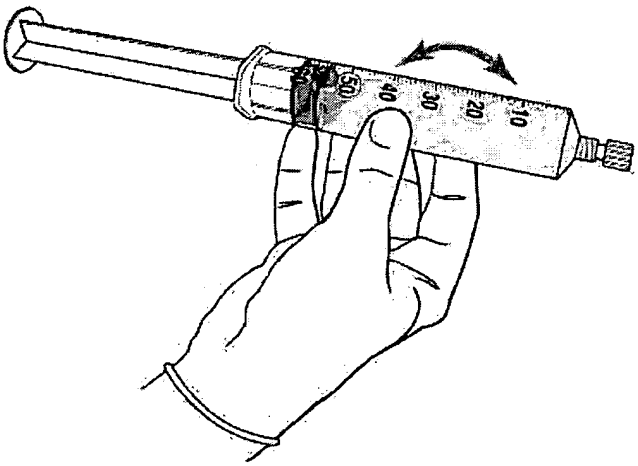


Figure 5.

5. Remove the needle from the powder vial, disconnect the needle from the syringe tip and discard it. Plug the syringe with the syringe cap (Figure 5). Gently mix the contents of the syringe. The reconstituted solution of Cysview is colorless to pale yellow and clear to slightly opalescent, and free from visible particles.

Figure 6.

6. Peel off the detachable portion of the label (starting at the corner marked with a black triangle) from the Cysview powder vial and affix it to the syringe containing the solution of Cysview (Figure 6). Add two hours to the present time and write the resulting expiration time and date on the syringe label.

   Cysview is now reconstituted and ready for use. Instill the reconstituted solution of Cysview into the bladder. If unable to administer the solution shortly after reconstitution, the solution may be stored for up to 2 hours in a refrigerator at 2°-8°C (36°- 46°F) in the labeled syringe. If not used within 2 hours, discard the solution. (2.2, 16)

2.3 Bladder Instillation of Cysview

For bladder instillation of the solution of Cysview, use straight, or intermittent, urethral catheters with a proximal funnel opening that will accommodate the Luer Lock adapter. Use only catheters made of vinyl (uncoated or coated with hydrogel), latex (amber or red), and silicone to instill the reconstituted Cysview. Do not use catheters coated or embedded with silver or antibiotics. In-dwelling bladder catheters (Foley catheters) may be used if the catheters are inserted shortly prior to Cysview administration and are removed following the Cysview instillation.

Use the following steps for bladder instillation of Cysview:

1. Using standard sterile catheterization technique, first insert the urethral catheter into the bladder of the patient and use the catheter to completely empty the patient's bladder before instillation of Cysview.

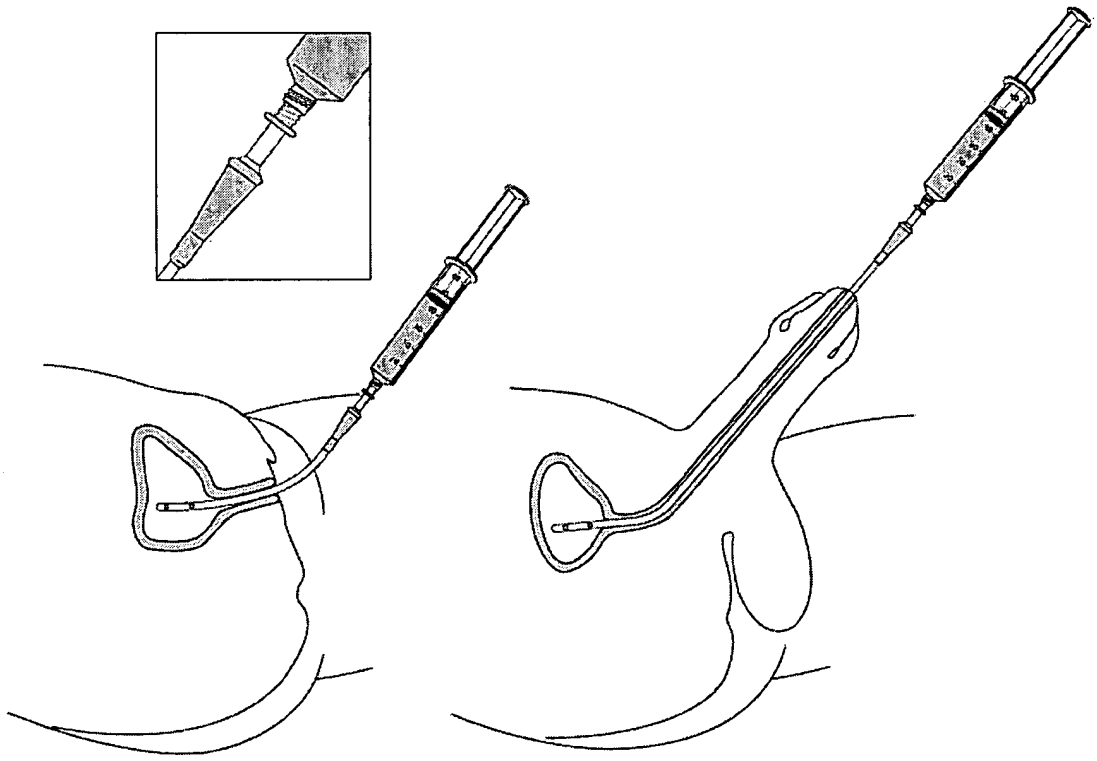


Figure 7.

2. To attach the syringe containing the solution of Cysview to the catheter, do the following:
   - Remove the syringe cap from the 50 mL syringe that contains the solution of Cysview.
   - Attach the Luer Lock end of the (provided) catheter adapter to the syringe.
   - Insert the tapered end of the catheter adapter into the funnel opening of the catheter. See Figure 7, with the connection enlarged in the inset.

3. Slowly instill the solution of Cysview into the bladder through the catheter (Figure 7), ensuring that the complete volume of the syringe (50 mL) is administered.

4. After the solution is instilled, remove the catheter and instruct the patient to retain the solution within the bladder for at least 1 hour; do not exceed 3 hours [*see Dosage and Administration (2.4)*]. Patients may stand, sit and move about during the time period between instillation and start of the cystoscopic procedure.

5. Evacuate the solution of Cysview from the bladder as part of routine emptying of the bladder immediately prior to the initiation of the cystoscopic procedure (refer to the Karl Storz PDD Telescope Instruction manual). Also, the patient may void and completely empty the bladder prior to the procedure.

Avoid skin contact with Cysview. If skin does come in contact with Cysview, wash immediately with soap and water and dry off. After voiding the bladder of Cysview, routinely wash the patient's perineal skin region with soap and water and dry.

2.4 Use of the Karl Storz D-Light C Photodynamic Diagnostic (PDD) System

Cysview imaging requires the use of the Karl Storz D-Light C PDD system, which consists of a light source, a camera and a telescope. The light source enables both white light cystoscopy and blue light (wavelength 360 – 450 nm) fluorescence cystoscopy. Familiarity with this system is essential before beginning the procedure and before instilling Cysview into the bladder. For system set up and general information for the safe use of the PDD system, refer to the Karl Storz instruction manual for the PDD system and the instruction manuals for each of the system components. The PDD System is not for use by healthcare providers with green-red color blindness.

2.5 Cystoscopic Examination

Training

Training and proficiency in cystoscopic procedures are essential prior to the use of Cysview. Carefully review the instruction manuals provided with the Karl Storz D-Light C Photodynamic Diagnosis (PDD) System. For additional training in the use of the PDD System, contact the manufacturer's representative.

Preparation for Cystoscopy

Initiate the cystoscopic examination within 30 minutes after evacuation of Cysview from the bladder, but no less than 1 or more than 3 hours after Cysview is instilled in the bladder. If the patient did not retain Cysview in the bladder for 1 hour, allow 1 hour to pass from the instillation of Cysview into the bladder to the start of the cystoscopic examination. The efficacy of Cysview has not been established when the solution was retained for less than 1 hour.

Cystoscopic Examination

Empty the patient's bladder and then fill the bladder with a clear fluid (standard bladder irrigation fluid) in order to distend the bladder wall for cystoscopic visibility. Ensure adequate irrigation during examination of the bladder; blood, urine or floating particles in the bladder may interfere with visualization under both white light and blue light.

First perform a complete cystoscopic examination of the entire bladder under white light (Mode 1) and then repeat the examination of the entire bladder surface under blue light (Mode 2) unless the white light cystoscopy reveals extensive mucosal inflammation. Do not perform the blue light cystoscopy if the white light cystoscopy reveals wide-spread mucosal inflammation. Abnormalities of the bladder mucosa during blue light cystoscopy are characterized by the detection of red, homogenous and intense fluorescence. The margins of the abnormal lesions are typically well-demarcated and in contrast to the normal urothelium, which appears blue. Register and document (map) the location and appearance (e.g. papillary) of suspicious lesions and abnormalities seen under either white or blue light.

During the cystoscopic examination, be aware that:

- a red fluorescence is expected at the bladder outlet and the prostatic urethra; this fluorescence occurs in normal tissue and is usually less intense and more diffuse than the bladder mucosal fluorescence associated with malignant lesions.
- tangential light may give false fluorescence. To help avoid false fluorescence, hold the endoscope perpendicular and close to the bladder wall with the bladder distended.
- false positive fluorescence may result from scope trauma from a previous cystoscopic examination and/or bladder inflammation *[see Warnings and Precautions (5.3)]*.
- malignant lesions may not fluoresce following Cysview administration, particularly if the lesions are coated with necrotic tissue. Blue light may fail to detect T2 tumors which have a tendency to be necrotic on the surface, and necrotic cells generally do not fluoresce *[see Warnings and Precautions (5.3)]*.
- when performing the blue light cystocopy, avoid prolonged blue light exposure. Studies have not evaluated the potential for adverse effects from blue light. In the controlled clinical trial, the cumulative blue light exposure from bladder mapping did not exceed 12 minutes and checking for complete tumor resection under blue light did not exceed 8 minutes for any patient *[see Clinical Studies (14)]*.

Perform biopsy and/or resection of suspicious lesions by transurethral resection of the bladder (TURB) only after completing white and blue light cystoscopic examinations with bladder mapping. Using standard cystoscopic practices, obtain biopsies of abnormal areas identified during either white or blue light examination and perform resections. Always check for the completeness of the resections under both white light and blue light before finalizing the TURB procedure.

3 DOSAGE FORMS AND STRENGTHS

Cysview (hexaminolevulinate hydrochloride) is supplied as a kit containing:

- Cysview *(hexaminolevulinate hydrochloride) for Intravesical Solution, 100 mg,* as a powder in a 10 mL clear glass vial.
- DILUENT for Cysview, 50 mL, in a polypropylene vial.
- One Luer Lock catheter adapter (to connect the syringe containing the reconstituted solution of Cysview to the urethral catheter for bladder instillation of Cysview).

Once reconstituted, the solution of Cysview contains 2 mg/mL of hexaminolevulinate hydrochloride.

4 CONTRAINDICATIONS

Cysview is contraindicated in patients with:

- porphyria
- gross hematuria
- BCG immunotherapy or intravesical chemotherapy within the past 90 days
- known hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

Anaphylaxis, including anaphylactoid shock, has been reported following administration of Cysview *[see Adverse Reactions (6.2)]*. Prior to and during use of the Cysview, have trained personnel and therapies available for the treatment of anaphylaxis. The safety of repetitive Cysview exposures has not been evaluated.

5.2 Failed Detection

Cysview may fail to detect some bladder tumors, including malignant lesions. Cysview is not a replacement for random biopsies or any other procedure usually performed in the cystoscopic evaluation for cancer. In the controlled clinical trial, Cysview failed to detect 10% of lesions confirmed as malignant within the study drug group *[see Clinical Studies (14)]*. Do not perform cystoscopy with blue light alone as malignant lesions can be missed unless the bladder is initially examined under white light *[see Dosage and Administration (2.5)]*.

5.3 False Fluorescence

Fluorescent areas detected during blue light cystoscopy may not indicate a bladder mucosal lesion. In the controlled clinical study, biopsies from one of every four fluorescent areas showed neither dysplasia nor carcinoma, if the areas were not also identified during white light cystoscopy *[see Clinical Studies (14)]*. In addition to these false detections, fluorescent areas within the bladder mucosa may result from inflammation, cystoscopic trauma, scar tissue or bladder mucosal biopsy from a previous cystoscopic examination.

The presence of urine and/or blood within the bladder may interfere with the detection of tissue fluorescence. To enhance the diagnostic utility of Cysview with the Karl Storz D-Light C PDD System:

- ensure the bladder is emptied of urine prior to the instillation of fluids at cystoscopy;
- biopsy/resect bladder mucosal lesions only following completion of both white light and blue light cystoscopy;

6 ADVERSE REACTIONS

Anaphylaxis has been reported following exposure to Cysview *[see Warnings and Precautions (5.1)]*.

6.1 Clinical Study Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In six clinical trials, safety data were obtained from 1,324 patients, aged 32 to 96 years with a median age of 69 years, all primarily Caucasian and approximately 75% male. All patients were evaluated after a single instillation of 50 mL solution of Cysview. Of these patients, 161 (12.2%) patients reported at least one adverse reaction. The most common adverse reaction was bladder spasm (reported in 2.2% of the patients) followed by dysuria, hematuria, and bladder pain. No patients experienced anaphylaxis. In the controlled clinical study, adverse reactions were similar in nature and rate between the study drug group and the control group *[see Clinical Studies (14)]*.

6.2 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Anaphylactoid shock, hypersensitivity reactions, bladder pain, cystitis and abnormal urinalysis have been reported during post-marketing use of Cysview.

7 DRUG INTERACTIONS

No specific drug interaction studies have been performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Adequate reproductive and developmental toxicity studies in animals have not been performed. Cysview should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether hexaminolevulinate is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when Cysview is administered to nursing mothers.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of 1823 subjects in clinical studies of Cysview, 67% were 65 years and over while 34% were 75 years and over. No clinically important differences in safety or efficacy have been observed between older and younger patients in the controlled study.

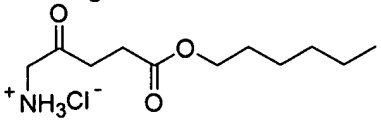
10 OVERDOSAGE

No adverse events were reported in a dose-finding study conducted among patients whose bladders were instilled with twice the recommended concentration (dose) of solution of Cysview.

11 DESCRIPTION

Cysview contains hexaminolevulinate hydrochloride, an optical imaging drug that in solution form is instilled intravesically for use with photodynamic blue light cystoscopy as an adjunct to white light cystoscopy.

The chemical formula for hexaminolevulinate hydrochloride is $C_{11}H_{21}NO_3 \cdot HCl$. Its molecular weight is 251.76 and it has the following structural formula:



Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution is intended for intravesical administration only after reconstitution with the supplied 50 mL DILUENT. Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution and DILUENT for Cysview are supplied together as a kit.

Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution is supplied as a sterile, non-pyrogenic, freeze-dried, white to off-white or pale yellow, powder containing 100 mg of hexaminolevulinate hydrochloride (equivalent of 85 mg of hexaminolevulinate) in a 10 mL clear glass vials. The DILUENT for Cysview is a sterile, non-pyrogenic solution (pH 6) containing 0.61 mg/ mL disodium hydrogen phosphate, 0.58 mg/mL of potassium dihydrogen phosphate, 7.02 mg/mL of sodium chloride, hydrochloric acid, sodium hydroxide, and water for injection. It is a clear, colorless solution, free from visible particles, and is provided in a 50 mL polypropylene vial.

The reconstituted solution of Cysview contains 2 mg/ml of hexaminolevulinate hydrochloride and is colorless to pale yellow. It is free from visible particles and has a pH between 5.7 and 6.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cysview is an ester of the heme precursor, aminolevulinic acid. After bladder instillation, Cysview enters the bladder mucosa and is proposed to enter the intracellular space of mucosal cells where it is used as a precursor in the formation of the photoactive intermediate protoporphyrin IX (PpIX) and other photoactive porphyrins (PAPs). PpIX and PAPs are reported to accumulate preferentially in neoplastic cells as compared to normal urothelium, partly due to altered enzymatic activity in the neoplastic cells. After excitation with light at wavelengths between 360 and 450 nm, PpIX and other PAPs return to a lower energy level by fluorescing, which can be detected and used for cystoscopic detection of lesions. The fluorescence from tumor tissue appears bright red and demarcated, whereas the background normal tissue appears dark blue. Similar processes may occur in inflamed cells.

12.2 Pharmacodynamics

In vitro studies have shown increased porphyrin fluorescence in normal urothelium after exposure to Cysview. In the human bladder, a greater accumulation of porphyrins is proposed in neoplastic or inflamed cells, compared to normal urothelium. After bladder instillation of Cysview for approximately 1 hour and subsequent illumination with blue light at wavelengths 360 – 450nm, the porphyrins will fluoresce red *[see Dosage and Administration (2.5)]*.

12.3 Pharmacokinetics

After bladder instillation of [^{14}C]-labeled Cysview (100 mg) for approximately 1 hour in healthy volunteers, absolute bioavailability of Cysview was 7% (90% confidence interval [CI]: 5%-10%). The [^{14}C]-labeled substance(s) showed biphasic elimination, with an initial elimination half-life of 39 minutes, followed by a terminal half-life of approximately 76 hours. Whole blood analysis showed no evidence of significant binding of Cysview to erythrocytes. An *in vitro* study showed that Cysview underwent rapid metabolism in human blood.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies in animals have been conducted to evaluate the carcinogenic potential of hexaminolevulinate hydrochloride.

Hexaminolevulinate hydrochloride was not mutagenic in *in vitro* reverse mutation tests in bacteria, or in chromosome aberration tests in human peripheral blood lymphocytes, and was negative in an *in vivo* micronucleus test in mice after intravenous injection of doses up to 45 mg/kg in the absence of light activation. Adequate studies have not been performed to evaluate the genetic toxicity of hexaminolevulinate hydrochloride in the presence of light activation.

Adequate reproductive and developmental toxicity studies in animals have not been performed to evaluate the effects of hexaminolevulinate hydrochloride on fertility.

13.2 Animal Toxicology and/or Pharmacology

Dose dependent neurological effects such as tremor, increased motor activity, and increased startle and touch escape responses were observed immediately after dosing at doses ≥ 30 mg/kg (24 times human systemic exposure based on the body surface area, using 10% as the upper level of 90% confidence interval of bioavailability) in a single dose rat study. The animals recovered to normal status by 60 min after dosing. Adverse neurological effects were also noted in other single or repeat dose toxicity studies.

Hexaminolevulinate hydrochloride had moderate to strong potential to cause skin sensitization based on a local lymph node assay in mouse.

14 CLINICAL STUDIES

The safety and efficacy of Cysview when used with photodynamic cystoscopy were studied in a prospective, multicenter, controlled clinical trial. Adult patients with known or suspected bladder cancer were randomized to either white light (WL) cystoscopy (control group, n = 384) or WL followed by blue light (BL) cystoscopy (study drug group, n = 395). Only the study drug group patients received Cysview by bladder instillation prior to cystoscopy. After bladder evacuation of Cysview, bladder lesion mapping was performed initially using the Karl Storz PDD system in the WL mode followed by lesion mapping in the BL mode. Control group patients underwent only WL cystoscopy with lesion mapping. The average age of the randomized patients was 69 years (range 24 to 96); 78% were male and 94% were Caucasian. All patients had previously undergone cystoscopy.

The main diagnostic efficacy outcome was assessed within the study drug group. This assessment compared lesions detected during an initial cystoscopic examination to their centralized histologic findings (the standard of truth). Following the initial diagnostic cystoscopy, patients within both study groups who had histologically confirmed Ta and/or T1 lesions underwent follow-up WL cystoscopy at 3, 6 and 9 months; these histologic evaluations were based upon the site assessments at both the initial and follow-up cystoscopy.

Diagnostic efficacy assessed the number of patients within the study drug group who had at least one additional Ta or T1 bladder cancer detected only by BL; the proportion of these patients was compared to a proposed threshold proportion of 10%. Within the study drug group, 286 patients had at least one Ta and/or T1 lesion, including 47 patients who had at least one of the lesions detected only by BL (see Table 1).

Table 1: BL Cystoscopic Ta and/or T1 Lesion Detection within the Study Drug Group

Number of patients with any Ta and/or T1 lesion detected with either WL or BL	286
Number (%) of patients with any Ta and/or T1 lesion detected only with BL	47 (16%)
p-value*	0.001

*exact test comparison of the proportion to a threshold value of 10%

Some malignant lesions were detected only by WL or BL (see Table 2).

Table 2: Bladder Tumor Detection within the Study Drug Group by WL and/or BL Cystoscopy

Number of lesions	Detected by Both WL & BL	Detected by WL Only	Detected by BL Only
CIS, n = 66	33	6	27
Ta, n = 580	472	52	56
T1, n = 95	76	10	9
T2 – T4, n = 47	38	8	1

Among the lesions detected only by BL, 23% were negative for any carcinoma-related pathology, including dysplasia. Among the lesions detected only by WL, 17% were negative for any carcinoma-related pathology, including dysplasia.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cysview is supplied as a kit labeled, Cysview (hexaminolevulinate hydrochloride) Kit for Intravesical Solution, 100 mg. The kit contains:

- One vial of Cysview (hexaminolevulinate hydrochloride) for Intravesical Solution, 100 mg, as a powder in a 10 mL clear glass vial.
- One vial of DILUENT for Cysview, 50 mL, in a polypropylene vial.
- One Luer Lock catheter adapter (to connect the syringe containing Cysview solution to the urethral catheter during instillation of Cysview)

NDC 0407-4085-01

Storage

Store Cysview (hexaminolevulinate hydrochloride) Kit for Intravesical Solution at 20°-25°C (68°-77°F); excursions are permitted to 15°-30°C (59°-86°F). Do not use beyond the expiry date printed on the carton.

Use the solution of Cysview shortly after reconstitution. If unable to use within this time period, the reconstituted solution can be stored under refrigeration (2°-8°C / 36°-46°F) for up to 2 hours in the 50 mL labeled syringe.

17 PATIENT COUNSELING INFORMATION

Ask patients if they have:

- a diagnosis or a family history of porphyria
- allergy to aminolevulinic acid or prior exposure to Cysview
- gross hematuria
- had BCG immunotherapy or chemotherapy within the bladder.

Inform patients that Cysview should be retained in the bladder for 1 hour from instillation of Cysview to the start of the cystoscopic procedure. If the patient cannot hold Cysview for 1 hour, but needs to void and expel Cysview from the bladder, he or she may void and should then inform a health care professional *[see Dosage and Administration (2)]*.

Distributed by GE Healthcare Inc., Princeton, NJ 08540 U.S.A.
Licensed from Photocure ASA.

Packaged and Labeled by Orifice Medical AB, Ystad, Sweden.

43-4085

Exhibit C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

STATEMENT UNDER 37 C.F.R. § 3.73(b) AND APPOINTMENT OF AGENT CONCERNING APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156

The ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE states that it is a partial assignee of the right, title, and interest in the below identified patent, owning 43% thereof, by virtue of an assignment by three of the seven inventors thereof, Matthieu Zellweger, Georges Wagnières, and Hubert van den Bergh. A true copy of the original assignment is attached hereto.

The ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE does hereby appoint PHOTOCURE ASA, having offices at

Hoffsveien 48
NO-0377 Oslo
Norway

as its agent to further the application for patent term extension under 35 U.S.C. § 156 concerning the below identified patent.

TITLE OF INVENTION	:	Solution for Diagnosing or Treating Tissue Pathologies
PATENT NUMBER	:	7,348,361
FILING DATE	:	April 22, 1999
ISSUE DATE	:	March 25, 2008
INVENTORS	:	Marti *et al.*
APPLICANT'S AGENT	:	Photocure ASA
ADDRESS	:	Hoffsveien 48 NO-0377 Oslo Norway

The undersigned, whose title is supplied below, is authorized to act on behalf of the assignee.

ÉCOLE POLYTECHNIQUE FÉDÉRALE
DE LAUSANNE
CH-1015 Lausanne
Switzerland

DATE: June 30, 2010 SIGNATURE: _____

Name: Françoise CHARDONNENS
Title: Legal Counsel of the
École Polytechnique Fédérale de Lausanne

NITROS P146US

ASSIGNMENT OF INVENTION

For: ☐ U.S. and/or ☐ Foreign Rights
For: ☒ U.S. Application or ☐ U.S. Patent
By: ☒ Inventor(s) or ☐ Present Owner

Assignment Recorded on
_____
Reel: _____
Frame: _____

In consideration of the payment by ASSIGNEE to ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration,

ASSIGNOR: Matthieu ZELLWEGER
Chemin des Cottages 10
CH - 1007 LAUSANNE
Switzerland

hereby sells, assigns and transfers to ASSIGNEE:

ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE
CH - 1015 LAUSANNE
Switzerland

and the successors, assigns and legal representatives of the ASSIGNEE

- ☒ the entire right, title and interest
- ☐ an undivided _____ percent (___%) interest for the United States and its territorial possessions
- ☐ and in all foreign countries, including all rights to claim priority,

in and to any and all improvements which are disclosed in the invention entitled,

SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES

and which is found in

- ☐ U.S. Patent Application executed on even date herewith; or
- ☐ U.S. Patent Application executed on _____; or
- ☒ U.S. Application serial no. 09/673,871 filed on April 22, 1999 (may be filled in when known); or
- ☐ U.S. Patent No. _____ issued _____;
- ☐ A change of address to which correspondence is to be sent regarding patent maintenance fees is being sent separately; or
- ☐ and any legal equivalent thereof in a foreign country, including the right to claim priority;

and, in and to, all Letters Patent to be obtained for said invention by the above application or any continuation, division, renewal, or substitute thereof, and as to letters patent any reissue or re-examination thereof;

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment;

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said invention and said Letters Patent and legal equivalents as may be known and accessible to ASSIGNOR and will testify as to the same in any interference, litigation or proceeding related thereto and will promptly execute and deliver to ASSIGNEE or its legal representatives any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalents thereof which may be necessary or desirable to carry out the purposes thereof.

IN WITNESS WHEREOF, I/We have hereunto set hand this

Date: Sept 25th, 2002 _____

If ASSIGNOR is a legal entity complete the following information

_____ _____
Name of person authorized to sign on behalf of ASSIGNOR | Title

NITROS P146US

ASSIGNMENT OF INVENTION

For: ☐ U.S. and/or ☐ Foreign Rights
For: ☒ U.S. Application or ☐ U.S. Patent
By: ☒ Inventor(s) or ☐ Present Owner

Assignment Recorded on _____
Reel: _____
Frame: _____

In consideration of the payment by ASSIGNEE to ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration,

ASSIGNOR: Georges WAGNIERES
Chemin de la Brume 6
CH - 1110 MORGES
Switzerland

hereby sells, assigns and transfers to ASSIGNEE:

ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE
CH - 1015 LAUSANNE
Switzerland

and the successors, assigns and legal representatives of the ASSIGNEE

- ☒ the entire right, title and interest
- ☐ an undivided _____ percent (___%) interest for the United States and its territorial possessions
- ☐ and in all foreign countries, including all rights to claim priority,

in and to any and all improvements which are disclosed in the invention entitled,

SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES

and which is found in

- ☐ U.S. Patent Application executed on even date herewith; or
- ☐ U.S. Patent Application executed on _____; or
- ☒ U.S. Application serial no. 09/673,871 filed on April 22, 1999 (may be filled in when known); or
- ☐ U.S. Patent No. _____ issued _____;
- ☐ A change of address to which correspondence is to be sent regarding patent maintenance fees is being sent separately; or
- ☐ and any legal equivalent thereof in a foreign country, including the right to claim priority;

and, in and to, all Letters Patent to be obtained for said invention by the above application or any continuation, division, renewal, or substitute thereof, and as to letters patent any reissue or re-examination thereof;

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment;

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said invention and said Letters Patent and legal equivalents as may be known and accessible to ASSIGNOR and will testify as to the same in any interference, litigation or proceeding related thereto and will promptly execute and deliver to ASSIGNEE or its legal representatives any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalents thereof which may be necessary or desirable to carry out the purposes thereof.

IN WITNESS WHEREOF, I/We have hereunto set hand this

Date: 21st of September 2002 _____

If ASSIGNOR is a legal entity complete the following information

_____ Name of person authorized to sign on behalf of ASSIGNOR

_____ Title

NITROS P146US

ASSIGNMENT OF INVENTION

For: ☐ U.S. and/or ☐ Foreign Rights
For: ☒ U.S. Application or ☐ U.S. Patent
By: ☒ Inventor(s) or ☐ Present Owner

Assignment Recorded on _____
Reel: _____
Frame: _____

In consideration of the payment by ASSIGNEE to ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration,

ASSIGNOR: Hubert VAN DEN BERGH
La Bergerie
CH - 1376 GOUMOENS-LA-VILLE
Switzerland

hereby sells, assigns and transfers to ASSIGNEE:

ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE
CH - 1015 LAUSANNE
Switzerland

and the successors, assigns and legal representatives of the ASSIGNEE

☒ the entire right, title and interest
☐ an undivided _____ percent (___%) interest for the United States and its territorial possessions
☐ and in all foreign countries, including all rights to claim priority,

in and to any and all improvements which are disclosed in the invention entitled,

SOLUTION FOR DIAGNOSING OR TREATING TISSUE PATHOLOGIES

and which is found in

☐ U.S. Patent Application executed on even date herewith; or
☐ U.S. Patent Application executed on _____; or
☒ U.S. Application serial no. 09/673,871 filed on April 22, 1999 (may be filled in when known); or
☐ U.S. Patent No. _____ issued _____;
☐ A change of address to which correspondence is to be sent regarding patent maintenance fees is being sent separately; or
☐ and any legal equivalent thereof in a foreign country, including the right to claim priority;

and, in and to, all Letters Patent to be obtained for said invention by the above application or any continuation, division, renewal, or substitute thereof, and as to letters patent any reissue or re-examination thereof;

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment;

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said invention and said Letters Patent and legal equivalents as may be known and accessible to ASSIGNOR and will testify as to the same in any interference, litigation or proceeding related thereto and will promptly execute and deliver to ASSIGNEE or its legal representatives any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalents thereof which may be necessary or desirable to carry out the purposes thereof.

IN WITNESS WHEREOF, I/We have hereunto set hand this

Date: 21.09.00

_____

If ASSIGNOR is a legal entity complete the following information

_____ Name of person authorized to sign on behalf of ASSIGNOR

_____ Title

Exhibit D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

STATEMENT UNDER 37 C.F.R. § 3.73(b) AND APPOINTMENT OF AGENT CONCERNING APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156

I, Norbert Lange, do hereby state that I am a partial owner of the below identified patent, owning 14% thereof, by virtue of being one of seven inventors of the patent.

I, Norbert Lange, do hereby appoint Photocure ASA, having offices at

Hoffsveien 48
NO-0377 Oslo
Norway

as my agent to further the application for patent term extension under 35 U.S.C. § 156 concerning the below identified patent.

TITLE OF INVENTION	:	Solution for Diagnosing or Treating Tissue Pathologies
PATENT NUMBER	:	7,348,361
FILING DATE	:	April 22, 1999
ISSUE DATE	:	March 25, 2008
INVENTORS	:	Marti *et al.*
APPLICANT'S AGENT	:	Photocure ASA
ADDRESS	:	Hoffsveien 48 NO-0377 Oslo Norway

Norbert Lange
(*street address*) Chemin de Valmont 142
(*city*) 1260 Nyon
(*country*) Switzerland

DATE: July 1st 2010 SIGNATURE: _____

Name: Norbert Lange

Exhibit E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

STATEMENT UNDER 37 C.F.R. § 3.73(b) AND APPOINTMENT OF AGENT CONCERNING APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. § 156

The UNIVERSITY OF LAUSANNE states that it is a partial assignee of the right, title, and interest in the below identified patent, owning 43% thereof, by virtue of an assignment by three of the inventors thereof, Alexandre Marti, Patrice Jichlinski, and Pavel Kucera. A true copy of the original assignment is attached hereto.

The UNIVERSITY OF LAUSANNE does hereby appoint PHOTOCURE ASA, having offices at

Hoffsveien 48
NO-0377 Oslo
Norway

as its agent to further the application for patent term extension under 35 U.S.C. § 156 concerning the below identified patent.

TITLE OF INVENTION	:	Solution for Diagnosing or Treating Tissue Pathologies
PATENT NUMBER	:	7,348,361
FILING DATE	:	April 22, 1999
ISSUE DATE	:	March 25, 2008
INVENTORS	:	Marti *et al.*
APPLICANT'S AGENT	:	Photocure ASA
ADDRESS	:	Hoffsveien 48 NO-0377 Oslo Norway

The undersigned, whose title is supplied below, is authorized to act on behalf of the assignee.

UNIVERSITY OF LAUSANNE
Quartier Unil-Centre
Bâtiment Unicentre
1015 Lausanne
Switzerland

DATE: July 8th 2010 SIGNATURE: _____

Name: Philippe Moreillon
Title: Vice-Recteur of the University of Lausanne

Confidentiel

ASSIGNMENT AGREEMENT

concluded between on the one side

University of Lausanne, Quartier Unil-Centre, Bâtiment Unicentre, 1015 Lausanne, Switzerland, represented by Mr. Philippe Moreillon, Vice -Recteur of the University,

hereinafter referred to as "**Unil**"

and on the other side

Mr. Pavel Kucera, located at Chemin de la Ratavolar 8, 1000Lausanne 27, Switzerland

hereinafter referred to as « **Inventor** ».

The Unil and the Inventors may be hereinafter individually or jointly referred to as "the Party" or "the Parties".

The Parties declares the following:

A. According to the agreement "Règlement sur la gestion du domaine de l'enseignement et de la recherché en biologie et en médecine par l'Université de Lausanne, les Hospice cantonaux et le Centre hospitalier universitaire vaudois" concluded between the Centre hospitalier universitaire vaudois –CHUV- and the University of Lausanne, CHUV's patents are filed and administered by the University of Lausanne in the name of the University of Lausanne.

B. On their own expense, the Inventors have filed with the co-inventors Mr. Matthieu Zellweger, Mr. George Wagnieres, Mr. Nobert Lange, Mr. Hubert Van den Bergh and Mr. Pavel Kucera (hereinafter referred to as (co-inventors) a patent applications PCT/CH99/00163 the April 22, 1999 (hereinafter referred to as the "Patent Application"). The invention concerns a 5-aminolevulinic acid ester (E-ALA) solution for producing a pharmaceutical preparation useful for diagnosing and/or treating tissues and/or pathologies by local radiation exposure using radiation emitted by a light source energy followed, in the case diagnosis, by detection of fluorescent protoporphyrin IX (Pp 1X) (hereinafter referred to as "Patent").

C. At the time the Invention was made, the Inventor was an employee of the Unil.

D. To be in accordance with the article 332 of the Swiss federal act of obligations (Code des obligations Suisse), Unil is interested in acquiring all right, title and interest of the Inventor in, to and under the Patent Application, and the Inventors have agreed to sell and assign such right, title and interest to the Unil.

E. The costs incurred by the Inventors and the co-inventors in prosecuting the Patent Applications prior to the date of last signature of this Agreement are already paid and will not be reimbursed by Unil.

Now therefore, the Parties hereto covenant and agree as follows:

ARTICLE I - DEFINITIONS

In this Agreement, the following terms shall have the following meaning:

1.1 **"Patent Application"** shall mean (i) the patent applications attached as Exhibit A hereto, any provisional or non-provisional applications related thereto, and any continuation, divisional, continuation-in-part or reissue of such applications, (ii) any letters patent issuing from such applications, (ii) any divisions, continuations, continuations-in-part, extensions, substitutions, reissues, re-examinations, renewals or the like of such patents, (iv) any confirmation patents, registration patents or patents of addition based on such patents and (v) any foreign counterparts of any of the foregoing.

1.2 **"Effective Date"** shall mean the date at which this Agreement is signed by all Parties.

1.3 **"EPFL"** shall mean Ecole polytechnique fédérale de Lausanne.

ARTICLE II - ASSIGNMENT AND SALE

2.1 The Inventor hereby assigns, sells and transfers to the Unil all their rights, titles and interests in, to and under the Patent Application in all countries of the world. The Parties, agree upon request to execute and deliver or cause to be executed and delivered all documents, instruments or affidavits and to perform or cause to be performed all such other acts that may be reasonably requested to procure to the other Party the benefit of the assignment and sale set forth above, including without limitation those documents and acts necessary or useful in the preparation, filing, prosecution and maintenance of the Patent Application. The Parties undertake to refrain from and cause to be refrained from all acts and/or actions that would in any way diminish the Unil's right, title and interest in, to and under the Patent Application.

2.2 As from the Effective Date, Unil shall be solely responsible to pay the Inventor part of any and all future costs related to the prosecution, maintenance and defence of the Patent. The costs related to the assignment of the Patent Application from the Inventor to the Unil shall also be solely paid by the Unil.

ARTICLE III - CONSIDERATION FOR THE ASSIGNMENT AND SALE

3.1 As consideration for the assignment, sale and transfer of all right, title and interest in, to and under the Patent Application hereunder, the Unil shall make the following payment to the Inventor: REDACTED

3.2 The payment under this agreement shall be made by transfer to:

REDACTED

3.3 All payments due and payable under this Agreement shall be paid in full, without deduction of taxes or other fees which may be imposed by any government (including VAT if any is due) and which shall be paid by Unil.

ARTICLE IV - REPRESENTATIONS AND WARRANTIES

4.1 The Inventor make no warranty of any kind, express or implied, statutory or otherwise, as to the Patent Application, which are assigned on an "as is" basis. Nothing in this Agreement, except of the provision of Article 4.2 and 4.3 hereunder, shall be construed as either an express or an implied warranty, statutory or otherwise, in particular (without limitation) with respect to:

(i) merchantability or fitness for a particular purpose of the concepts covered by the Patent Application;
(ii) title to or validity of claims of the Patent Application, issued or pending;
(iii) the fact that the use or exploitation of the Patent Application, or of any patent issued thereon shall not infringe intellectual property rights of third parties.

Inventor hereby waive to Unil, to the fullest extent of the law, any and all rights they may have towards third persons for any compensation, indemnity, legal and attorney's fees, costs, expenses or losses of any kind arising out of the use of the technology covered by the Patent Application.

4.2 The Inventor represent and warrant that they have sole and exclusive joint title to the Patent Application with EPFL, Mr. Nobert Lange and Mr. Pavel Kucera and that they hold an unencumbered and complete right to assign, sell and transfer their part of the Patent Application to the Unil. The Inventor further represent and warrant that they have granted no license or other rights under the Patent Application to any third party.

4.3 By the present, the Inventor transfer to Unil all their rights and duties arising out of the licence agreement concluded between, on the one side, Inventor and co-inventors, and on the other side, PhotoCure ASA of February 13, 2000, amended by the contract between, on the one side, EPFL, Inventors, Mr. Nobert Lange and Mr. Pavel Kucera and, on the other side, PhotoCure ASA (Annexe 2).

4.4 The Inventor warrants to inform the company PhotoCure ASA about the transfer of the rights to Unil. They warrants to assign the company PhotoCure ASA to pay to Unil the royalties arising out of the licence agreement mentioned under article 4.3 of this Agreement.

ARTICLE V- TERM

This Agreement shall be effective as of the Effective Date.

ARTICLE VI – MISCELLANEOUS

6.1 The Unil may assign this Agreement or any of its rights and obligations hereunder in whole or in part at any time with written notice for information of such assignment to the Inventors. This Agreement shall be binding upon the Parties hereto and their heirs and permitted successors and assigns.

6.2 This Agreement constitutes the entire agreement between the Parties relating to the subject matter hereof and supersedes all prior and contemporaneous negotiations, agreements, representations, understandings and commitments with respect thereto.

6.3 No terms or provisions of this Agreement shall be varied, extended or modified by any prior or subsequent statement, conduct or act of either of the Parties, except by a written instrument specifically referring to and executed in the same manner as this Agreement.

6.4 Any notice or other communication required or permitted to be made or given by either of the Parties pursuant to the Agreement shall be deemed made or given on the date of sending if sent by courier, costs prepaid, or upon confirmed transmission if sent by facsimile to the addresses or facsimile numbers here below written, or to such other addresses as may be designated subsequently by either of the Parties to the other in writing:

Confidentiel

In the case of the Unil:
PACTT
Bureau de transfert de technologies
Rue du Bugnon 21
1005 Lausanne

In the case of the Inventor:

Dr. Pavel Kucera

Phone: 021 784 20 90
e-mail : pkucera@unil.ch

6.5. If any provision of or obligation under this Agreement shall be invalid, illegal or unenforceable in any jurisdiction, the validity, legality and enforceability of the remaining provisions or obligations, or of such provision or obligation in any other jurisdiction, shall not in my way be affected or impaired thereby.

Article VII - APPLICABLE LAW AND JURISDICTION

7.1 This Agreement shall be governed by Swiss law.

7.2 Any dispute relating to this Agreement shall be submitted to the exclusive jurisdiction of the competent courts of Lausanne, Switzerland.

In witness whereof, the Parties hereto have caused this Agreement to be executed and delivered in six originals signed by the therefore authorised persons, as of the Effective Date.

Unil:
By:_____
Name: Mr. Philippe Moreillon
Title: Vice-Recteur of the University of Lausanne
Date: 18.06.2010

Inventor:
By:_____
Name: Mr. Pavel Kucera
Title: Professeur honoraire
Date: 27.2.2009

One original has to be sent to PACTT, Bureau de transfert des technologies, Rue du Bugnon 21, 1005 Lausanne, Switzerland.

Confidentiel

Annexe 1

Patent Applications:

1. US patent application no. 10/826,788

Annexe 2

The licence agreement concluded between, on the one side, Inventors and co-inventors, and on the other side, PhotoCure ASA of February 13, 2000, amended by the contract between, on the one side, EPFL, Inventors, Mr. Nobert Lange and Mr. Pavel Kucera and, on the other side, PhotoCure ASA

CONFIRMATORY ASSIGNMENT

between on the one side

University of Lausanne, Quartier Unil-Centre, Bâtiment Unicentre, 1015 Lausanne, Switzerland, represented by Mr. Philippe Moreillon, Vice-Recteur of the University,

hereinafter referred to as "**Unil**"

and on the other side

Mr. Alexandre Marti, located at

Ch. des Geais 8, CH-1218 Le Grand Saconnex, Switzerland
(*current post office address*)

and

Mr. Patrice Jichlinski, located at

Ch. du Chêne 8, CH-1052 Le Mont-sur-Lausanne, Switzerland
(*current post office address*)

hereinafter referred to as "**Inventors.**"

The Unil and the Inventors may be hereinafter individually or jointly referred to as "the Party" or "the Parties."

The inventors hereby confirm that, for good and valuable consideration, the receipt of which is hereby acknowledged, the inventors have assigned, sold, and transferred, and do hereby assign, sell, and transfer to **Unil** their entire right, title, and interest in, to and under the **Patent Application** as defined in the **Assignment Agreement**, a true copy of which **Assignment Agreement** is attached hereto as Exhibit 1 ("the Assignment"), the Assignment having been executed by **University of Lausanne** on or about July 4, 2007, by **Mr. Alexandre Marti** on or about January 30, 2007, and by **Mr. Patrice Jichlinski** on or about February 22, 2007

In witness whereof, the Parties hereto have caused this Confirmatory Assignment to be executed by the therefor authorized persons.

Unil:
By: _____ Date: July 8th, 2010
Name: **Mr. Philippe Moreillon**
Title: Vice-Recteur of the University of Lausanne

Inventors:

By: _____ Date: _____
Name: **Mr. Alexandre Marti**

By: _____ Date: July 5th, 2010
Name: **Mr. Patrice Jichlinski**

In witness whereof, the Parties hereto have caused this Confirmatory Assignment to be executed by the therefor authorized persons.

Unil:
By: _____ Date: July 8th, 2010
Name: **Mr. Philippe Moreillon**
Title: Vice-Recteur of the University of Lausanne

Inventors:
By: _____ Date: July 11th 2010
Name: **Mr. Alexandre Marti**

By: _____ Date: July 5th, 2010
Name: **Mr. Patrice Jichlinski**

EXHIBIT 1

ASSIGNMENT AGREEMENT

Confidentiel

ASSIGNMENT AGREEMENT

concluded between on the one side

University of Lausanne, Quartier Unil-Centre, Bâtiment Unicentre, 1015 Lausanne, Switzerland, represented by Mr. Philippe Moreillon, Vice -Recteur of the University,

hereinafter referred to as "**Unil**"

and on the other side

Mr. Alexandre Marti, located at Chemin Champ-Baron 12, 1209 Genève, Switzerland

and

Mr. Patrice Jichlinski, located at Chemin du Chêne 8, 1052 Le Mont-sur-Lausanne, Switzerland

hereinafter referred to as « **Inventors** ».

The Unil and the Inventors may be hereinafter individually or jointly referred to as "the Party" or "the Parties".

The Parties declares the following:

A. According to the agreement "Règlement sur la gestion du domaine de l'enseignement et de la recherché en biologie et en médecine par l'Université de Lausanne, les Hospice cantonaux et le Centre hospitalier universitaire vaudois" concluded between the Centre hospitalier universitaire vaudois –CHUV- and the University of Lausanne, CHUV's patents are filed and administered by the University of Lausanne in the name of the University of Lausanne.

B. On their own expense, the Inventors have filed with the co-inventors Mr. Matthieu Zellweger, Mr. George Wagnieres, Mr. Nobert Lange, Mr. Hubert Van den Bergh and Mr. Pavel Kucera (hereinafter referred to as co-inventors) a patent applications PCT/CH99/00163 the April 22, 1999 (hereinafter referred to as the "Patent Application"). The invention concerns a 5-aminolevulinic acid ester (E-ALA) solution for producing a pharmaceutical preparation useful for diagnosing and/or treating tissues and/or pathologies by local radiation exposure using radiation emitted by a light source energy followed, in the case diagnosis, by detection of fluorescent protoporphyrin IX (Pp 1X) (hereinafter referred to as "Patent").

C. At the time the Invention was made, the Inventors where employees of the CHUV.

D. To be in accordance with the article 332 of the Swiss federal act of obligations (Code des obligations Suisse), Unil is interested in acquiring all right, title and interest of the Inventors in, to and under the Patent Application, and the Inventors have agreed to sell and assign such right, title and interest to the Unil.

E. The costs incurred by the Inventors and the co-inventors in prosecuting the Patent Applications prior to the date of last signature of this Agreement are already paid and will not be reimbursed by Unil.

Now therefore, the Parties hereto covenant and agree as follows:

ARTICLE I - DEFINITIONS

In this Agreement, the following terms shall have the following meaning:

1.1 "**Patent Application**" shall mean (i) the patent applications attached as Exhibit A hereto, any provisional or non-provisional applications related thereto, and any continuation, divisional, continuation-in-part or reissue of such applications, (ii) any letters patent issuing from such applications, (ii) any divisions, continuations, continuations-in-part, extensions, substitutions, reissues, re-examinations, renewals or the like of such patents, (iv) any confirmation patents, registration patents or patents of addition based on such patents and (v) any foreign counterparts of any of the foregoing.

1.2 "**Effective Date**" shall mean the date at which this Agreement is signed by all Parties.

1.3 "**EPFL**" shall mean Ecole polytechnique fédérale de Lausanne.

ARTICLE II - ASSIGNMENT AND SALE

2.1 The Inventors hereby assigns, sells and transfers to the Unil all their rights, titles and interests in, to and under the Patent Application in all countries of the world. The Parties, agree upon request to execute and deliver or cause to be executed and delivered all documents, instruments or affidavits and to perform or cause to be performed all such other acts that may be reasonably requested to procure to the other Party the benefit of the assignment and sale set forth above, including without limitation those documents and acts necessary or useful in the preparation, filing, prosecution and maintenance of the Patent Application. The Parties undertake to refrain from and cause to be refrained from all acts and/or actions that would in any way diminish the Unil's right, title and interest in, to and under the Patent Application.

2.2 As from the Effective Date, Unil shall be solely responsible to pay the Inventors part of any and all future costs related to the prosecution, maintenance and defence of the Patent. The costs related to the assignment of the Patent Application from the Inventors to the Unil shall also be solely paid by the Unil.

ARTICLE III - CONSIDERATION FOR THE ASSIGNMENT AND SALE

3.1 As consideration for the assignment, sale and transfer of all right, title and interest in, to and under the Patent Application hereunder, the Unil shall make the following payment to the Inventors: REDACTED

3.2 The payment under this agreement shall be made by transfer to:

REDACTED

3.3 All payments due and payable under this Agreement shall be paid in full, without deduction of taxes or other fees which may be imposed by any government (including VAT if any is due) and which shall be paid by Unil.

ARTICLE IV - REPRESENTATIONS AND WARRANTIES

4.1 The Inventors make no warranty of any kind, express or implied, statutory or otherwise, as to the Patent Application, which are assigned on an "as is" basis. Nothing in this Agreement, except of the provision of Article 4.2 and 4.3 hereunder, shall be construed as either an express or an implied warranty, statutory or otherwise, in particular (without limitation) with respect to:

(i) merchantability or fitness for a particular purpose of the concepts covered by the Patent Application;
(ii) title to or validity of claims of the Patent Application, issued or pending;
(iii) the fact that the use or exploitation of the Patent Application, or of any patent issued thereon shall not infringe intellectual property rights of third parties.

Inventors hereby waive to Unil, to the fullest extent of the law, any and all rights they may have towards third persons for any compensation, indemnity, legal and attorney's fees, costs, expenses or losses of any kind arising out of the use of the technology covered by the Patent Application.

4.2 The Inventors represent and warrant that they have sole and exclusive joint title to the Patent Application with EPFL, Mr. Nobert Lange and Mr. Pavel Kucera and that they hold an unencumbered and complete right to assign, sell and transfer their part of the Patent Application to the Unil. The Inventors further represent and warrant that they have granted no license or other rights under the Patent Application to any third party.

4.3 By the present, the Inventors transfer to Unil all their rights and duties arising out of the licence agreement concluded between, on the one side, Inventors and co-inventors, and on the other side, PhotoCure ASA of February 13, 2000, amended by the contract between, on the one side, EPFL, Inventors, Mr. Nobert Lange and Mr. Pavel Kucera and, on the other side, PhotoCure ASA (Annexe 2).

4.4 The Inventors warrants to inform the company PhotoCure ASA about the transfer of the rights to Unil. They warrants to assign the company PhotoCure ASA to pay to Unil the royalties arising out of the licence agreement mentioned under article 4.3 of this Agreement.

ARTICLE V- TERM

This Agreement shall be effective as of the Effective Date.

ARTICLE VI – MISCELLANEOUS

6.1 The Unil may assign this Agreement or any of its rights and obligations hereunder in whole or in part at any time with written notice for information of such assignment to the Inventors. This Agreement shall be binding upon the Parties hereto and their heirs and permitted successors and assigns.

6.2 This Agreement constitutes the entire agreement between the Parties relating to the subject matter hereof and supersedes all prior and contemporaneous negotiations, agreements, representations, understandings and commitments with respect thereto.

6.3 No terms or provisions of this Agreement shall be varied, extended or modified by any prior or subsequent statement, conduct or act of either of the Parties, except by a written instrument specifically referring to and executed in the same manner as this Agreement.

6.4 Any notice or other communication required or permitted to be made or given by either of the Parties pursuant to the Agreement shall be deemed made or given on the date of sending if sent by courier, costs prepaid, or upon confirmed transmission if sent by facsimile to the addresses or facsimile numbers here below written, or to such other addresses as may be designated subsequently by either of the Parties to the other in writing:
In the case of the Unil:
PACTT
Bureau de transfert de technologies
Rue du Bugnon 21
1005 Lausanne

In the case of the Inventors:

Dr. Patrice Jichlinski
8 chemin du Chêne
CH-1052 Le Mont sur Lausanne
Phone: +4121 652 16 16
Fax : +4121 652 16 69

Dr. Marti Alexandre
Chemin Champ-Baron 12
CH- 1209 Genève
Phone:
Fax :

6.5. If any provision of or obligation under this Agreement shall be invalid, illegal or unenforceable in any jurisdiction, the validity, legality and enforceability of the remaining provisions or obligations, or of such provision or obligation in any other jurisdiction, shall not in my way be affected or impaired thereby.

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In witness whereof, the Parties hereto have caused this Agreement to be executed and delivered in six originals signed by the therefore authorised persons, as of the Effective Date.

Unil:
By:_____

Name: Mr. Philippe Moreillon
Title: Vice-Recteur of the University of Lausanne
Date:

Inventors:

By:_____ By:_____

Name: Mr. Alexandre Marti
Title:
Date:

Name: Mr. Patrice Jichlinski
Title:
Date:

One original has to be sent to PACTT, Bureau de transfert des technologies, Rue du Bugnon 21, 1005 Lausanne, Switzerland.

Annexe 1

Patent Applications:

1. US patent application no. 10/826,788

Annexe 2

The licence agreement concluded between, on the one side, Inventors and co-inventors, and on the other side, PhotoCure ASA of February 13, 2000, amended by the contract between, on the one side, EPFL, Inventors, Mr. Nobert Lange and Mr. Pavel Kucera and, on the other side, PhotoCure ASA

Exhibit F

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

POWER OF ATTORNEY
CONCERNING APPLICATION FOR PATENT TERM EXTENSION
UNDER 35 U.S.C. § 156

PHOTOCURE ASA, being the duly authorized agent of the owners of the entire right, title, and interest of the below described patent in the application for extension of the patent's term under 35 U.S.C. § 156, does hereby appoint Deborah A. Somerville (Registration No. 31,995) and the practitioners associated with **CUSTOMER NO. 26646** as its attorneys/agents, with full power of substitution and revocation, to act on its behalf before the U.S. Patent and Trademark Office and to receive all communications and notices relative thereto in connection with the application for patent term extension concerning the below identified patent.

TITLE OF INVENTION	:	Solution for Diagnosing or Treating Tissue Pathologies
PATENT NUMBER	:	7,348,361
FILING DATE	:	April 22, 1999
ISSUE DATE	:	March 25, 2008
INVENTORS	:	Marti *et al.*
APPLICANT'S AGENT	:	Photocure ASA
ADDRESS	:	Hoffsveien 48 NO-0377 Oslo Norway

Please address all communications regarding this application for patent term extension to:

Deborah A. Somerville
KENYON & KENYON LLP
One Broadway
New York, New York 10004
Telephone: (212) 425-7200
Facsimile: (212) 425-5288
CUSTOMER NO. 26646

Please direct all telephone calls regarding this application for patent term extension to Deborah A. Somerville, (212) 425-7200.

The undersigned, whose title is supplied below, is authorized to act on behalf of PHOTOCURE ASA.

PHOTOCURE ASA
Hoffsveien 48
NO-0377 Oslo
Norway

Dated: 30 June 2010

By: _____

Name: **Insa Flechsler, Ph.D.**

Title: IP Director

Exhibit G

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): IND 51.224

Serial no	Date (dd.mm.yy)	Item
-	23.08.00	Request for Pre-IND Meeting incl. Pre-IND summary
FDA	07.09.00	Type B meeting granted
-	18.09.00	Pre-IND Meeting - Briefing Document, attendants
FDA	18.10.00	FDA Meeting minutes 18.10.00 Pre-IND meeting
FDA	05.12.00	CDRH comments following 18.10.00 pre-IND meeting
FDA	07.12.00	FDA Minutes of t-con 07.12.00 (need for autoradiographic studies)
000	29.10.01	IND
FDA	07.12.01	Minutes of t-con 07.12.01
001	13.12.01	Histopathol 7 days tolerance study
003	19.12.01	PC B302/01 protocol w/Amd 2
002	20.12.01	Minutes of t-con 07.12.01
FDA	07.01.02	Comments from clinical review, also discussed 07.12.01
004	14.01.02	PC perspective on use of random biopsies (B302 and B301)
005	14.01.02	Response to questions (by telephone) 11.01.02 re PC B301/01
FDA	21.01.02	Pharmacology/toxicology Response submitted 08.03.02
-	30.01.02	T-con regarding design of PC B302/01 (role of random biopsies)
007	06.02.02	Request for end-of-phase II meeting
009	07.02.02	Confirmation of end-of-phase II meeting (18.04.02)
FDA	14.02.02	IND chemistry review comments Resent 01.04.02 Response submitted 07.05.02
008	20.02.02	PC Minutes of t-con 30.01.02
006	28.02.02	PC B302/01 Final protocol, Investigator information
010	08.03.02	Response to FDA fax 21.01.02
011	18.03.02	Briefing document for end-of-phase II meeting
FDA	22.03.02	Questions on device
FDA	01.04.02	CMC questions Originally sent 14.02.02 (?) Response submitted 07.05.02
FDA	18.04.02	End-of-Phase II meeting minutes
014	02.05.02	PC B302/01 Protocol design (for t-con 6.5.02)
FDA	06.05.02	Statistical comments to protocol 302 discussed at EOP2 meeting
-	06.05.02	T-con regarding serial #014 study design/clinical program
012	07.05.02	Responses to FDA fax 01.04.02 CMC questions
016	16.05.02	PC B302/01 New investigator
017	24.05.02	PC B302/01; PC B305/02; Clin dev program: Diagnosis for Carcinoma in situ – inclusion criteria
015	06.06.02	Adverse events 302
013	11.06.02	End-of-Phase II meeting minutes 18.04.02
020	20.06.02	SAE 302, not related
018	24.06.02	PC B302/01 Protocol w/Amendment 2 (24.06.02) FDA response 29.08.02

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): IND 51.224

Serial no	Date (dd.mm.yy)	Item
019	10.07.02	PC B302 New investigator
021	19.07.02	PC B305/02 – Patient populations and study aspects (protocol review)
FDA	29.08.02	Clinical comments to protocols PC B302 and PC B305 Responses provided 20.05.03
FDA	01.10.02	Statistical comments to protocols PC B302 and PC B305 Responses provided 20.05.03
022	29.10.02	Stability protocol DS
023	18.11.02	B302/01 New investigator
024	04.12.02	SAE reports 302
FDA	23.01.03	FDA review of AE reports
025	05.02.03	SAE report
026	10.02.03	Manufacturing at Ben Venue for clinical supplies
027	20.02.03	302 Amd 3 Comments from FDA 06.05.03
028	21.02.03	SAE report
029	10.03.03	SAE reports
030		Does not exist; see #033
031	28.03.03	Request for meeting
032	01.04.03	SAE report
033	22.04.03	New investigator 302
034	22.04.03	New investigator 302
FDA	06.05.03	Meeting granted
FDA	06.05.03	Comments to submission 027
035	13.05.03	Briefing document for meeting
036	20.05.03	Supplement to briefing document
037	02.06.03	Participants for mtg 09.06.03
FDA	04.06.03	Preliminary comments before meeting 09.06.03
FDA	09.06.03	Meeting minutes
038	24.06.03	Base NDA on 301, 302, 303 FDA comments received 08.09.03
039	11.07.03	Meeting minutes 09.06.03
040	24.07.03	305 protocol for review FDA comments received 08.09.03
041	24.07.03	SAE report
042	05.08.03	SAE reports 302
043	05.08.03	302 new and existing investigators
044?	13.08.03	New investigator 302
FDA	08.09.03	Comments to *subm 040* (305 prot), and *038* (new plan)
045	17.10.03	Meeting request
FDA	30.10.03	Meeting granted
046	11.11.03	Briefing document
047	13.11.03	Participants for mtg 25.11.03
FDA	25.11.03	FDA meeting minutes
048	15.12.03	Change of address, US agent
049	12.01.04	New 305 protocol for review
FDA	15.03.04	Comments to 305
050	-	*Does not exist*

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): IND 51.224

Serial no	Date (dd.mm.yy)	Item
051	02.06.04	Request for Type C mtg
052	07.06.04	Request for t-con; statistical issues in 305
FDA	10.06.04	Type C mtg granted
053	21.06.04	Type C mtg confirmation
054	30.06.04	IND Annual report
FDA	02.07.04	Request for t-con denied; response to questions in request
055	23.07.04	Pre-meeting package
FDA	04.08.04	Request for Clarification of meeting package and additional information prior to meeting
056 (#1)	17.08.04	Response to fax request dated 04.08.04
FDA	27.08.04	List of attendees at mtg
FDA	22.09.04	FDA mtg minutes Type C meeting 26.08.04
056 (#2)	13.10.04	General correspondence: Transfer of IND Regulatory Contact and Authorised Representative, US agent
057	20.10.04	Request for pre-NDA meeting
058	19.11.04	Pre-NDA meeting Package
FDA	17.12.04	Preliminary responses to Questions
059	12.01.05	Pre-NDA meeting minutes
FDA	24.01.05	FDA meeting minutes of Pre-NDA Mtg
060	31.01.05	Type A mtg request – waiver of reprotox studies
FDA	22.02.05	Preliminary response to 31.01.05 Type A mtg request
FDA	15.03.05	Final response to 31.01.05 Type A mtg request
061	18.04.05	IND Annual report
NA	05.05.05	Request for Orphan Drug Designation
	17.06.05	Orphan Drug Designation request denied
062	20.12.05	15-days safety report
063	04.01.06	= 062 resent to new division
064	08.02.06	IND Safety Report: Follow-up to Written Report
065	27.02.06	Second Follow-up Written Report to 15-Day Safety Report
066	01.03.06	Corrected Second Follow-up Written Report to 15-Day Safety Report
067	29.03.06	IND Annual Report
068	11.10.06	IND Safety Report: Follow-up #3 Written Report
069	07.12.06	Type A Meeting Request – Discussion of PC B305/04 Statistical Analysis Plan
070	20.12.06	Type C Meeting Package - Discussion of SAP
NA	14.02.07	Responses to clinical questions in Type A mtg request dated 7 Dec 06
071	19.02.07	Confirmation of SAP discussion t-con
072	28.02.07	Type C Mtg Minutes SAP Discussion
073	02.03.07	IND Annual report
NA	14.03.07	Meeting minutes 15 March 2007
074	15.03.07	CD-ROM copy of SN0072
075	22.03.07	Type C mtg minutes – corrected version, discussion part
076	3 April 07	Chronological table of changes to protocol PCB305/04

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): IND 51.224

Serial no	Date (dd.mm.yy)	Item
077	05.04.07	IND Annual report
NA	07.05.07	Corrected meeting minutes from mtg 15 feb 02 – Clinical
078	27.06.07	Safety
079	01.10.07	Safety
081	03.12.07	Follow-up after Feb 15th 2007 t-con
082	31.01.08	Type C meeting request
NA	14.02.08	Type C meeting scheduled
083	03.03.08	IND Annual report
084	14.03.08	Background package
085	08 Apr 2008	Toxicology Protocol for Dog Study proposed to CDRH
NA	16.04.08	FDA draft response to 14 March 2008 meeting package
086	05 June 08	Sponsor Responses to 16 April 2008 FDA Meeting Response
087	13 June 08	FDA-requested electronic copy of SN 0086
088	10 Jul 2008	Type C Meeting Request Letter
NA	25 July 2008	Meeting request denial
089	31 Jul 2008	Sponsor Response to 25 July 2008 Meeting Request Denial Letter
NA	1 Aug 2008	FDA photobleaching comment (ref. 16 Apr comments)
090	07 Aug 2008	IND Safety Report: Initial Written Report
091	28 Aug 2008	Response FDA photobleaching comment of Aug 1st
092	4 Sept 2008	Safety issue D-Light C response to CDRH
093	12 Sept 2008	Signed protocol PC B304/04 submission
094	1 Oct 2008	Meeting Request
	16 Oct 2008	Type B meeting scheduled
095	16 Dec 2008	Briefing package submission
NA	27 Jan 2009	Preliminary meeting response
096	2 Feb 2009	Photocure Meeting minutes 29 Jan meeting
	4 Feb 2009	FDA decision re. requirement for NDA submission
097	12 Feb 2009	Request for t-con
	18 Feb 2009	Type B t-con granted
NA	24 Feb 2009	FDA Meeting minutes 29 Jan meeting
098	2 March 2009	Briefing package submission
099	13 March 2009	IND Annual report
100	16 March 2009	Submission of CDRH t-con meeting minutes re. submission of complete response to PMA issue
NA	31 March 2009	Preliminary meeting response
NA	3 April 2009	FDA meeting minutes
NA	3 April 2009	CDRH-amended minutes re. response to PMA question of 1 April tcon
101	20 May 2009	eCTD description and NDA number request
102	28 January 2010	IND Annual report
103	02 Mar 2010	Submission of electronic copies of Annual Report (December 1, 2008 – November 30, 2009)

Exhibit H

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): NDA 22-555

Type of Corresp.	FDA Contact	Serial #	Date	Description of Correspondence
email	T.Nguyen	[redacted]	01 Apr 09	Number of Copies for Upcoming Original NDA Submission
email	CDER	[redacted]	07 May 09	Request for a Pre-assigned eCTD NDA Number
submission	[redacted]	#0000	30 Jun 09	Initial NDA (Including priority review request)
email	T.Scott	[redacted]	20 Jul 09	FDA Request for Application Orientation Meeting (Meeting held on 06 Aug 09)
letter	T.Scott	[redacted]	20 Jul 09	FDA Request for Application Orientation Meeting
email	T.Scott	[redacted]	24 Jul 09	Foreign Visitor Forms for Application Orientation Meeting
email	T.Scott	[redacted]	28 Jul 09	Photocure Meeting Attendees for Application Orientation Meeting
email	T.Scott	[redacted]	05 Aug 09	Presentation Slides for Application Orientation Meeting
email	D.Henry	[redacted]	13 Aug 09	CMC Request for Additional Establishment Information (Submission #0001)
email	S.Kress	[redacted]	17 Aug 09	Request for Location in Application for list of Investigation Sites for PC B305/04 (Info emailed to FDA on 17 Aug 09)
email	T.Scott	[redacted]	17 Aug 09	List of FDA Attendees at Application Orientation Meeting
submission	[redacted]	#0001	20 Aug 09	Revised 356h and Attachment of Establishment Information
email	C.Carr	[redacted]	21 Aug 09	Proprietary Name Guidance (Submission #0002)
letter	T.Scott	[redacted]	24 Aug 09	Confirmation of Priority Review Designation and Fileability (Letter received by mail on 28 Aug 09)
submission	[redacted]	#0002	25 Aug 09	Request for Proprietary Name Review
email	J.Mulinde	[redacted]	25 Aug 09	Request for Clinical Site Contact Info and Location of Study Related Sponsor Records (Info emailed to FDA on 26 Aug 09)
email	S.Kress	[redacted]	26 Aug 09	Questions on Tables in Module 5
email	J.Mulinde	[redacted]	27 Aug 09	FDA Reply to CATO's response to FDA's request for PC B305 Site Contact Info and Location of TMF
email	S.Kress	[redacted]	27 Aug 09	Additional Questions on Tables in Module 5 (Cato called FDA to discuss questions on 27 Aug 09)
email	T.Scott	[redacted]	28 Aug 09	Notification of Upcoming Advisory Committee Meeting for Hexvix (Meeting to be held in Dec 09)
email	S.Kress	[redacted]	02 Sep 09	Question Regarding Efficacy Data for Clinical Study PC B305 (Info emailed on 03 Sep 09)
email	S.Kress	[redacted]	03 Sep 09	CATO Response to Question Regarding Efficacy Data for Clinical Study PC B305
email	N.Vesely	[redacted]	04 Sep 09	Notification of ODAC Meeting on 17 December 2009
letter	N.Vesely	[redacted]	04 Sep 09	Notification of ODAC Meeting on 17 December 2009
submission	[redacted]	#0003	08 Sep 09	Photocure Meeting Minutes of the Meeting on 06 August 2009, along with Meeting Presentation
email	T.Scott	[redacted]	11 Sep 09	FDA Response to Submission of an Electronic Video File and Request for Submission of PMA Amendment (Submission #0005 and #0006)
letter	T.Nguyen	[redacted]	11 Sep 09	Day 74 FDA Filing Letter (Submission #0007)

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): NDA 22-555

Type of Corresp.	FDA Contact	Serial #	Date	Description of Correspondence
submission	[redacted]	#0004	15 Sep 09	European Guidelines for the Use of Hexvix Fluorescence Cystoscopy; CMC Information Update: In Process Bioburden Method for Hexvix Powder
email	M.White	[redacted]	16 Sep 09	FDA Announcement of Site-Sponsor Inspections
letter	M.White	[redacted]	16 Sep 09	FDA Announcement of Site-Sponsor Inspections
email	T.Nguyen	[redacted]	18 Sep 09	Day 74 FDA Filing Letter
email	M.White	[redacted]	22 Sep 09	FDA Request for Hotel Information for Site-Sponsor Inspections (Info emailed on 24 Sep 09)
submission	[redacted]	#0005	22 Sep 09	Notice of Submission of DVD (Hexvix Mode of Action - EU Version) Desk Copies to Thuy Nguyen
email	M.White	[redacted]	24 Sep 09	CATO Response to FDA Request for Hotel Information for Site-Sponsor Inspections
submission	[redacted]	#0006	25 Sep 09	Copy of PMA 050027/A018 – Complete Response Submission
email	N.Vesely	[redacted]	30 Sep 09	CATO Response to FDA Request for Investigator List for ODAC Meeting
email	T.Nguyen	[redacted]	01 Oct 09	Request for Clinical Information on SAE Reports (Submission #0009)
email	S.Kress	[redacted]	06 Oct 09	CATO Response to FDA Request for Add Info on Anaphylactic Shock SAE Report
submission	[redacted]	#0007	06 Oct 09	Response to FDA Request for Information – Filing Communication Letter dated 11 September 2009
email	T.Nguyen	[redacted]	07 Oct 09	Request for Email Correspondence on Anaphylactic Shock SAE Report be Formally Submitted to FDA (Submission #0008)
email	M.White	[redacted]	08 Oct 09	CATO Response to FDA Request for Ground Transport for Site-Sponsor Inspections
email	M.White	[redacted]	08 Oct 09	Additional CATO Response to FDA Request for Ground Transport for Site-Sponsor Inspections
submission	[redacted]	#0008	09 Oct 09	Email Correspondence of 6 October 2009 between Dr. Kress and Dr. Hughes
email	T.Nguyen	[redacted]	13 Oct 09	Request for Additional Pharm-Tox Info on Reproductive-Developmental Tox Studies (Submission #0010)
email	T.Nguyen	[redacted]	13 Oct 09	Request for Statistical Teleconference and Information (T-Con held on 15 Oct 09)
submission	[redacted]	#0009	13 Oct 09	Complete Response to FDA Clinical Information Request of 01 October 2009
email	T.Nguyen	[redacted]	14 Oct 09	Request for Additional Statistical Information (Submission #0011)
email	N.Vesely	[redacted]	15 Oct 09	CATO Response to FDA Request for Address to Ship FDA ODAC Meeting Briefing Package
submission	[redacted]	#0010	15 Oct 09	Complete Response to FDA Pharmacology/Toxicology Information Request of 13 October 2009
email	T.Nguyen	[redacted]	16 Oct 09	CATO Response to FDA Request for Clinical Information on False Positives and Biopsies
email	T.Nguyen	[redacted]	16 Oct 09	CATO Response to FDA Request for Draft Package Insert Teleconference (T-Con held on 19 Oct 09)

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): NDA 22-555

Type of Corresp.	FDA Contact	Serial #	Date	Description of Correspondence
email	T.Nguyen	[redacted]	19 Oct 09	CATO Response to FDA Request for Draft Package Insert in Editable Format (Submission #0012)
email	L.Adams	[redacted]	21 Oct 09	Notification of FDA Inspection of Fresenius and Request for Contact Info (CATO called FDA on 21 Oct 09)
submission	[redacted]	#0011	21 Oct 09	Complete Response to FDA Statistical Information Request of 14 October 2009 and Clinical Information Request of 15 October 2009 ()
email	T.Nguyen	[redacted]	22 Oct 09	CATO Response to FDA Request for Carton and Container Label in Editable Format (Submission #0014)
submission	[redacted]	#0012	22 Oct 09	Email Correspondence of 19 October 2009 between Ms. Nguyen and Dr. Hughes Regarding Microsoft Word Version of Draft Package Insert ()
submission	[redacted]	#0013	23 Oct 09	120-Day Safety Update
email	L.Adams	[redacted]	28 Oct 09	Request for CD Copy of Module 3 (CD mailed to FDA on 29 Oct 09)
submission	[redacted]	#0014	29 Oct 09	Complete Response to FDA Label Information Request of 21 October 2009 - Information Provided by Email
email	N.Vesely	[redacted]	02 Nov 09	ODAC Meeting Attendees
email	N.Vesely	[redacted]	02 Nov 09	ODAC Meeting Briefing Package Reminder
email	T.Nguyen	[redacted]	02 Nov 09	FDA Clinical Information Request
email	T.Nguyen	[redacted]	03 Nov 09	FDA Clinical Information Request
email	T.Nguyen	[redacted]	03 Nov 09	PHC Response to FDA Clinical Information Request of 02 Nov 09 (Submission #0015)
email	T.Nguyen	[redacted]	03 Nov 09	PHC Response to FDA Clinical Information Request of 03 Nov 09 (Submission #0015)
email	T.Nguyen	[redacted]	04 Nov 09	FDA Clinical Information Request
submission	[redacted]	#0015	04 Nov 09	Complete Response to FDA Clinical Information Request of 02 November 2009 and 03 November 2009 – Information Provided by Email on 03 November 2009
email	T.Nguyen	[redacted]	05 Nov 09	FDA Statistical Information Request (Submission #0016)
email	T.Nguyen	[redacted]	06 Nov 09	PHC Response to FDA Clinical Information Request of 04 Nov 09 (Submission #0016)
submission	[redacted]	#0016	09 Nov 09	Complete Response to FDA Clinical Information Request of 04 November 2009 and Statistical Information Request of 05 November 2009 – Information Provided by Email
email	T.Nguyen	[redacted]	10 Nov 09	FDA Pharm-Tox Information Request (Submission #0017)
fax	C.Carr	[redacted]	10 Nov 09	Proprietary Name Request Unacceptable
submission	N. Vesely	[redacted]	12 Nov 09	Briefing Document for 17 December 2009 Oncologic Drugs Advisory Committee Meeting
email	N. Vesely	[redacted]	13 Nov 09	ODAC Meeting PHC Presentation Time
email	N. Vesely	[redacted]	15 Nov 09	ODAC Meeting Briefing Package - Should not be Confidential
email	N. Vesely	[redacted]	16 Nov 09	ODAC Federal Register Notice and Meeting Logistics
email	T.Nguyen	[redacted]	16 Nov 09	FDA Statistical Information Request (Submission #0017)
submission	N. Vesely	[redacted]	17 Nov 09	Revised Briefing Document for 17 December 2009 Oncologic Drugs Advisory Committee Meeting

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): NDA 22-555

Type of Corresp.	FDA Contact	Serial #	Date	Description of Correspondence
email	N. Vesely	[redacted]	18 Nov 09	FDA Confirmed Receipt of ODAC Meeting Briefing Package
submission	[redacted]	#0017	19 Nov 09	Complete Response to FDA Pharmacology/Toxicology Comments of 10 November 2009 and Statistical Information Request of 16 November 2009
submission	[redacted]	#0018	20 Nov 09	Request for Proprietary Name Review
email	N. Vesely	[redacted]	24 Nov 09	FDA Tracking Number for FDA ODAC Background Package
email	N. Vesely	[redacted]	30 Nov 09	Draft Agenda for ODAC Meeting
email	N. Vesely	[redacted]	30 Nov 09	ODAC Meeting - Financial Relationship
email	T.Nguyen	[redacted]	01 Dec 09	Comments on FDA ODAC Briefing Package
email	T.Nguyen	[redacted]	01 Dec 09	FDA Request for Face to Face Meeting with PHC
email	T.Nguyen	[redacted]	02 Dec 09	FDA Statistical Information Request (Submission #0019)
email	T.Nguyen	[redacted]	03 Dec 09	FDA CMC and Labeling Information Request (Submission #0019 and #0021)
email	T.Nguyen	[redacted]	03 Dec 09	FDA Statistical Information Request
email	N.Vesely	[redacted]	04 Dec 09	FDA ODAC Meeting Briefing Package - PHC Changes Accepted
email	T.Nguyen	[redacted]	08 Dec 09	Logisitics and Meeting Attendees for 09 Dec 09 FDA Meeting - Kit Demonstration
email	T.Nguyen	[redacted]	08 Dec 09	PHC Response to FDA Clinical Information Request of 07 Dec 09 (Submission #0019)
email	N.Vesely	[redacted]	09 Dec 09	Final FDA ODAC Dcouments
email	T.Nguyen	[redacted]	09 Dec 09	FDA Information Request from Kit Demonstration
email	T.Nguyen	[redacted]	09 Dec 09	FDA Statistical Information Request (Submission #0021)
submission	[redacted]	#0019	09 Dec 09	Complete Response to FDA Statistical Information Request of 02 December 2009; Chemistry Information Request of 03 December 2009 and Clinical Information Request of 07 December 2009
email	T.Nguyen	[redacted]	10 Dec 09	FDA CMC and Labeling Information Request
email	T.Nguyen	[redacted]	10 Dec 09	FDA Statistical Information Request
email	T.Nguyen	[redacted]	10 Dec 09	PHC Response to FDA Statistical Information Request of 09 Dec 09 (Submission #0021)
email	T.Nguyen	[redacted]	11 Dec 09	PHC Response to FDA CMC Information Request of 03 Dec 09 (Submission #0019 and #0021)
email	T.Nguyen	[redacted]	11 Dec 09	PHC Response to FDA Statistical Information Request of 10 Dec 09 (Submission #0021)
email	T.Nguyen	[redacted]	14 Dec 09	Final List of FDA and CATO Meeting Attendees for 09 Dec 09 FDA Meeting - Kit Demonstration
email	T.Nguyen	[redacted]	14 Dec 09	PHC Response to FDA CMC Information Request of 10 Dec 09 (Submission #0021)
email	N.Vesely	[redacted]	15 Dec 09	Posted ODAC Meeting Douments
email	T.Nguyen	[redacted]	15 Dec 09	Proposed Proprietary Names for Hexvix (Submission #0020)
email	T.Nguyen	[redacted]	15 Dec 09	Sponsor Prepared Meeting Minutes from 09 Dec 09 Meeting
submission	[redacted]	#0020	16 Dec 09	New Proposed Proprietary Names for Hexaminolevulinate Hydrochloride

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): NDA 22-555

Type of Corresp.	FDA Contact	Serial #	Date	Description of Correspondence
submission	[redacted]	#0021	17 Dec 09	Sponsor-prepared meeting minutes of FDA meeting of 09 December 2009; Complete Response to FDA Statistical Information Request of 09 December 2009, Statistical Information Request of 10 December 2009, Chemistry Information Request of 03 December 2009 - Questions 5 and 6, and Chemistry Information Request of 10 December 2009
submission	[redacted]	#0022	18 Dec 09	Withdrawal of Reconsideration of Proprietary Name Review
submission	[redacted]	#0023	22 Dec 09	Response to Chemistry Information Request of 03 December 2009 – CMC Comment # 5
email	T.Nguyen	[redacted]	22 Dec 09	PHC Additional Response to FDA CMC Information Request of 10 Dec 09
email	T.Nguyen	[redacted]	24 Dec 09	FDA Meeting Minutes from 09 Dec 09 Meeting
email	T.Nguyen	[redacted]	30 Dec 09	FDA Complete Response Letter
email	C.Carr	[redacted]	08 Jan 10	FDA Teleconference - Proprietary Name Discussion
email	C.Carr	[redacted]	11 Jan 10	Revised Preference Order for List of Proposed Proprietary Names
submission	[redacted]	#0024	11 Jan 10	Request for Face-to-Face Type B Meeting
email	C.Carr	[redacted]	14 Jan 10	FDA Attendees at 11 Jan 10 Teleconference
email	C.Carr	[redacted]	14 Jan 10	Withdrawal of Proprietary Name Review Request dated 16 Dec 09 (Submission #0025)
email	T.Nguyen	[redacted]	14 Jan 10	FDA Granted Type B Meeting
submission	[redacted]	#0025	14 Jan 10	Withdrawal of Request for Proprietary Name Review Dated 16 December 2009
email	T.Nguyen	[redacted]	29 Jan 10	Proprietary Name Review
submission	[redacted]	#0026	02 Feb 10	Meeting Information Package for 03 March 2010 Type B Face-to-Face Meeting
email	T.Nguyen	[redacted]	04 Feb 10	Foreign Visitor Forms for 03 March 10 FDA Meeting
email	T.Nguyen	[redacted]	04 Feb 10	Receipt of Meeting Package for 03 March 10 FDA Meeting
submission	[redacted]	#0027	10 Feb 10	Request for Proprietary Name Review
submission	[redacted]	#0028	17 Feb 10	Additional patent information submitted in Form FDA 3542a
email	T.Nguyen	[redacted]	23 Feb 10	Final List of Attendees for 03 March 10 FDA Meeting
email	T.Nguyen	[redacted]	26 Feb 10	FDA Preliminary Meeting Responses for 03 March 10 FDA Meeting
submission	[redacted]	#0029	08 Mar 10	Electronic presentation presented by Photocure at 03 March 2010 Type B Meeting
submission	[redacted]	#0030	12 Mar 10	Photocure Meeting Minutes of the Type B Meeting held on 03 March 2010, along with Meeting Presentation
email	T.Nguyen	[redacted]	30 Mar 10	FDA Meeting Minutes for 03 March 10 FDA Meeting
submission	[redacted]	#0031	31 Mar 10	Resubmission - Photocure's Complete Response to FDA Complete Response Letter of 30 December 2009 and Re-confirmation of Request for Proprietary Name Review submitted on 10 February 2010 in Amendment 0027
email	T.Nguyen	[redacted]	06 Apr 10	PHC Response to FDA Request for Word Versions of Labels

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): NDA 22-555

Type of Corresp.	FDA Contact	Serial #	Date	Description of Correspondence
submission	[redacted]	#0032	09 Apr 10	FDA Requested Microsoft Word Versions of Carton and Container Labels
letter	T.Nguyen	[redacted]	26 Apr 10	FDA Acknowledgement of Class I Resubmission
email	T.Nguyen	[redacted]	06 May 10	FDA Labeling Information Request
email	T.Nguyen	[redacted]	07 May 10	FDA Labeling Information Request
email	T.Nguyen	[redacted]	07 May 10	PHC Questions and Comments from 06 and 07 May 10 FDA Labeling Information Request
email	T.Nguyen	[redacted]	07 May 10	FDA Responses to PHC Questions and Comments from 06 and 07 May 10 FDA Labeling Information Request
email	T.Nguyen	[redacted]	10 May 10	PHC Confirmation to Formally Submit Email Correspondence
Letter	C.Holquist	[redacted]	10 May 10	Notification of Proprietary Name Request Conditionally Acceptable-Cysview
email	T.Nguyen	[redacted]	17 May 10	PHC Response to FDA Labeling Information Request of 06 and 07 May 10 (Submission #0033)
submission	[redacted]	#0033	17 May 10	Complete Response to FDA Labeling Information Request of 06 May 2010 and FDA Label Comments\Information Request of 07 May 2010
email	T.Nguyen	[redacted]	19 May 10	FDA Labeling Information Request
email	T.Nguyen	[redacted]	20 May 10	PHC Response to FDA Labeling Information Request of 19 May 10
submission	[redacted]	#0034	20 May 10	Complete Response to FDA Labeling\Label and Post-Marketing Commitment Information Request of 19 May 2010
email	T.Nguyen	[redacted]	25 May 10	Revised Carton and Container Labels
submission	[redacted]	#0035	25 May 10	Complete Response to FDA Request of 25 May 2010 regarding Revised Carton
email	T.Nguyen	[redacted]	26 May 10	FDA Labeling Information Request
email	T.Nguyen	[redacted]	26 May 10	PHC Response to FDA Labeling Information Request of 26 May 10 (Submission #0036)
submission	[redacted]	#0036	26 May 10	Complete Response to FDA Label/Labeling Information Request of 26 May 2010
email	**T.Nguyen**	[redacted]	**28 May 10**	**FDA CDER Regulatory Action Letter - NDA Approval**
email	S.Lange	[redacted]	02 Jun 10	Draft Burst Email from FDA for PHC Review
email	T.Nguyen	[redacted]	02 Jun 10	New FDA Project Manager
email	S.Lange	[redacted]	03 Jun 10	PHC Comments on Draft Burst Email from FDA
submission	[redacted]	#0037	11 Jun 10	SPL for approved NDA 22-555
	[redacted]			

Exhibit I

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): NDA 21-893

FDA Request date (dd.mm.yy)	Amd no	Amd date (dd.mm.yy)	Item
08.07.05	-		Administrative
03.08.05 fax	001	09.08.05	Clinical
04.08.05 t-con	001	09.08.05	Clinical
03.08.05 fax	003	16.08.05	CMC – CFN numbers
04.08.05 fax	003	16.08.05	CMC – CFN numbers and readiness for inspection
09.08.05 fax	002	12.08.05	Clinical – study 302
17.08.05 tel, 18.08.05 tel	006	23.08.05	CMC
17.08.05 tel, 18.08.05 tel *cont.*	004	18.08.05	CMC/Clinical
17.08.05 tel, 18.08.05 tel *cont.*	Tel	17.08.05 Lynda Sutton	Clinical
18.08.05 tel	004	18.08.05	CMC
09.08.05 fax	005	19.08.05	Clinical
22.08.05 tel	006	23.08.05	CMC
24.08.05 tel	007	25.08.05	Drug-Device
24.08.05 tel	007	25.08.05	CMC
26.08.05 tel	008	02.09.05	Administrative
01.09.05 (received 12.09.05)	009	27.09.05	Filing communication – Clinical
-	009	27.09.05	Administrative - Huntsman DMF #2517 for NDA section 1.4.1
13.09.05	NA	29.09.05	DSI Compliance – Clinical site inspection
14.09.05	NA	15.09.05	Administrative – additional copies Mod 1
27.09.05 tel	010	28.09.05	Administrative - labeling
27.09.05	011	30.09.05	Administrative – cover letter to DSI

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): NDA 21-893

FDA Request date (dd.mm.yy)	Amd no	Amd date (dd.mm.yy)	Item
tel			
18.10.05 fax	014	03.11.05	Compliance – Clinical site inspection
19.10.05 tel	012	21.10.05	Administrative - labeling
21.10.05 tel	012	21.10.05	Administrative - labeling
NA (General require-ment)	013	28.10.05	Administrative – 120-days safety update
NA	NA	30.11.05	PDUFA fee waiver request
21.11.05 tel	015	06.12.05	CMC – BV DMF #2315
01.12.05 fax	016	12.12.05	Pharmacology/ Toxicology
NA	NA	30.11.05/ 02.12.05	PDUFA Fee Waiver Request
14.12.05 fax	017/018	20.12.05	(Administrative – NDA copy)
14.12.05 fax *cont.*	018	20.12.05	Clinical/Device
14.12.05 fax *cont.*	018	20.12.05	Clinical/Device
NA	019	20.12.05	Safety
20.12.05 – 21.12.05 t-con + fax (to be answered together with request dated 22.12.05)	020	03.01.06	Clinical - pathology
22.12.05 fax	020	03.01.06	Clinical - pathology
23.12.05 fax	021	09.01.06	CMC

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): NDA 21-893

FDA Request date (dd.mm.yy)	Amd no	Amd date (dd.mm.yy)	Item
23.12.05 fax *cont.*	021	09.01.06	CMC *Question 8 cont.*
23.12.05 fax	022	11.01.06	CMC – Microbiology; Ben Venue
11.01.06 fax RETRAC-TED same date	NA	NA	Clinical - pathology
12.01.06 tel	024	16.01.06	Administrative – NDA copy
12.01.06 fax	023	16.01.06	Statistical Clinical – Pathology
12.01.06 fax	025 see also follow-up response Amd *034?*	18.01.06 see also follow-up response *XX*.03.06	Pharmacology/Toxicology
19.01.06 tel	028	26.01.06	CMC
23.01.06 tel	027	25.01.06	CMC – Microbiology
24.01.06 fax	026	25.01.06	CMC
02.02.06 fax	NA	03.02.06 fax	CMC
NA	029 (028 on cover letter)	08.02.06	Safety
17.02.06 tel	030	22.02.06	CMC
22.02.06 fax	031	27.02.06 fax, 28.02.06 official hard copy	CMC
NA	NA	20.02.06	Orphan status
NA	032 034	24.02.06? 28.02.06?	Safety
28.02.06	033	28.02.06 fax, 01.03.06 official hard copy	Pharmacology/ Toxicology
(12.01.06)	035	16.03.06	Pharmacology/ Toxicology

Brief Description of Representative Significant Activities During the Regulatory Period for Hexvix® (Cysview™ (hexaminolevulinate hydrochloride) for Intravesical Solution): NDA 21-893

FDA Request date (dd.mm.yy)	Amd no	Amd date (dd.mm.yy)	Item
22.03.06	036	22.03.06 fax, 23.03.06 hard copy	Clinical
13.04.06	NA	NA	Orphan
19.04.06			Action letter; non-approval
	037	26.04.06	Response to not-approvable letter
	038	04.08.06	Permission for GE to communicate with FDA
	039	24.08.06	Request for meeting
	040		
	041	11.10.06	Safety
	042	12.10.06	Request for t-con on 16 Oct 06
	043	17.10.06	Additional information for End-of-Review t-con on 26 Oct 2006
	044	23.10.06	Request for Type C meeting See Response to non-clinical issues in fax from FDA dated 14 Feb 2007
25.10.06	NA	NA	Meeting response to clinical questions
	045	27.10.06	Request to maintain End-of-Review t-con
	046	30.10.06	Request to revise agenda for Type C mtg
06.11.06			Minutes of End-of-Review t-con 26 Oct 2006
19.11.06	NA	NA	Scheduled t-con to discuss focus of upcoming t-con to discuss clinical issues in not-approvable letter
20.11.06	NA	NA	Scheduled t-con to discuss CMC, preclinical issues in not-approvable letter
	047	13.11.06	Type C meeting request
	048	28.11.06	Minutes of End-of-Review t-con 26.10.06
	049	19.12.06	Meeting package
14.02.07	NA	NA	Responses to nonclinical questions
	050	12.02.07	Cancellation of t-con, nonclinical
NA	051	27.06.07	Safety
	052	01.10.07	Safety
	053	07.08.07	Safety